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TREATMENT RESEARCH MONOGRAPH SERIES

RESEARCH ON THE TREATMENT OF NARCOTIC ADDICTION

State of the Art

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

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RESEARCH ON THE TREATMENT OF NARCOTIC ADDICTION

State of the Art

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

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INTRODUCTION

During the last 15 years, much has been written on the safety and efficacy of methadone for the treatment of opiate dependency. Even more information has been generated on the effectiveness of methadone maintenance as a treatment modality. During this same time, several other related events were occurring. By 1974, the National Institute on Drug Abuse (NIDA) was receiving an increasing number of requests for clinical technical assistance from both new methadone programs and State drug treatment agencies. The methadone-treatment modality was relatively new but growing; hence many clinicians had no prior education or clinical experience in the field, although many were eager to learn. Perhaps most apparent was their interest in learning the current state of the art with respect to a number of related clinical issues. As the number of methadone treatment clinics grew, so did the number of critics. Some of the criticism was warranted and expected because of the problems associated with developing a new treatment program for high risk patients. However, much of the criticism was often antithetical to scientifically generated data.

During the last 10 years, the National Institute on Drug Abuse has had the opportunity to collect and analyze the information required to respond to program and State requests for technical assistance, and to the critics. It gradually became apparent that there was a considerable amount of information (sometimes unpublished and often conflicting) on methadone-related treatment issues. The research design and methodologies of the studies which generated these results varied in quality, which often made comparison of the results difficult. Moreover, a reference did not exist that attempted to resolve these differences and delineate the existing state of the art.

Recognizing the need for a reference on methadone treatment, an advisory group was formed for the purposes of determining the content and the most effective method for reviewing and interpreting the available information, and disseminating such a document to the field. The advisory group consisted of NIDA staff who were most familiar with the basic and clinical research results on the use of methadone for the treatment of opiate addiction. After considerable thought and debate, the group decided to hold three symposia on narcotic addiction treatment. In each symposium the state of the art was reviewed and discussed

with respect to three different general aspects of narcotic treatment: effects of methadone and other narcotics on users and offspring; technical and clinical issues associated with narcotic maintenance and detoxification treatment; and patient and treatment variables affecting outcome. The general and specific areas for review as well as symposium participants were selected by the advisory group.

Each symposium provided a forum for a general discussion among all participants of each of the topics reviewed in this book. A general discussion followed presentation of a prepared review and analysis of the literature and (when available) unpublished grant or contract results pertaining to the issue. In addition, a prepared critique of the review paper was presented before the general discussion. At the end of the general discussion of each topic, areas of agreement were defined, along with a rationale for any disagreement regarding the clinical significance of the reviewed information. Moreover, when there was a consensus regarding specific future research needs or strong belief of a participant that future research was required, these areas were noted.

This book has been organized in much the same way the symposia were conducted. The book is divided into three parts; the content corresponds to the issues reviewed, critiqued, and discussed at each symposium. Each specific issue reviewed, critiqued, and discussed, is a chapter. There are several exceptions. Drs. Cicero, Hutchings, and Zagon, who did not attend, were asked to review and comment on the clinical significance of the preclinical behavioral and biochemical studies of methadone and other narcotics. Likewise, Dr. Hall was asked to contribute her chapter subsequent to the symposia. Consequently, there is no discussion summary following her review. Mr. Rachal and Dr. Hubbard attended the symposium on treatment outcome and subsequently provided the TOPS information. The editors thought that since this information was new and relevant to part III, it should be included.

It is hoped that this broad review will accomplish several purposes. It should provide the physician with technical guidance on a number of clinical issues. Part I addresses clinical issues and attempts to answer the clinical questions NIDA is more frequently asked. Precise and practical guidance is provided (with unanimous consensus of the participants) on the use of psychotropic drugs for treating patients with concomitant DSM III illnesses. The

vigorous analytic review of the literature and the subsequent group consensus regarding methadone dose and duration provide an excellent reference for making these types of clinical decisions. This particular chapter has additional relevance with the knowledge that in September 1980, 41 percent of the 63,559 patients in maintenance treatment were stabilized on less than 40 mg of methadone.* The information on detoxification in general and the use of specific drugs in particular should help the clinician decide on a preferred detoxification regimen and on the usefulness of these drugs in clinical practice.

The medical and scientific information reviewed in part II further demonstrates the safety of methadone. There was unanimous agreement that the drug is safe when used by physicians knowledgeable in the treatment of narcotic addiction. No major adverse consequences of prolonged methadone use have ever been consistently demonstrated. The review of the genetic, reproductive, and teratogenic studies (much of which is heretofore unpublished) reveals that there is no convincing evidence that methadone is teratogenic. Moreover, a review of the preclinical methadone studies suggests that there are no major adverse consequences of prolonged use of this drug in humans, a finding consistent with clinical experience.

The information presented in part III provides a foundation for further research to attempt to define the specific program/patient variables affecting outcome. For example, there was agreement that outcome is affected by the patient's relationship to some aspect of the program (in addition to methadone), but whether it is the counselor's efforts, daily attendance required to obtain methadone, and/or special service programs (legal, educational, vocational, or psychotherapeutic) remains to be determined. Interestingly, the available data suggest that for most patients psychotherapy is neither attractive nor necessary to achieve positive outcome. The recent work of McLellan et al.** provides a model for the design of studies that can address the efficacy of other treatment/rehabilitation initiatives. If these results are replicated in other clinics utilizing a prospective

* National Drug Abuse Treatment Utilization Survey, September 1980.

**McLellan, A.T.; Luborsky, L; Woody, G.E.; and O'Brien, C.P. Predicting response to alcohol and drug abuse treatments: Role of psychiatric severity. Arch Gen Psychiatry, 40:620-628, 1983.

design, the information will provide guidance for assigning certain types of treatment for certain types of drug dependent patients.

The information contained in the book further supports the effectiveness of methadone and the maintenance modality. Evaluation studies have consistently demonstrated that the longer a patient remains in treatment, irrespective of the treatment modality, the greater the likelihood of effecting a positive change in functioning and the more likely that gains will be sustained after treatment. Of all the available modalities for treating opiate addicts, the methadone modality has consistently retained the greatest proportion of admissions for the longest period of time. Not surprisingly, the dramatic impact on patients is seen during the actual treatment experience. The evidence presented regarding methadone maintenance indicates that while patients remain in treatment, their illicit opiate use and criminal behavior are significantly reduced. Most studies indicate that employment increases as well, albeit less dramatically than the other indicators. Since there is considerable evidence that higher doses improve retention, especially early in treatment, and result in lower levels of illicit opiate and other drug use, the use of methadone itself was considered to positively affect treatment outcome.

Lastly, the book provides the clinician or program/State administrator with the necessary medical and scientific facts for establishing policy regarding therapeutics and justifying continued program operation. There has been a growing trend over the last several years for States and programs to limit the maximum methadone dose and/or the duration of treatment for all patients. The information presented in this book indicates that such actions are therapeutically unjustified. More recently, as State financial treatment resources tighten, some have suggested cuts in methadone program funding based on a lack of demonstrated effectiveness. The clinical and evaluation research reported here do not support such a rationale. To argue that methadone maintenance is not at least as effective as other available modalities for treating this population is to ignore the results of the best designed research studies and the consensus of a varied group of experts in the drug/mental health field.

What follows is the state of the art as viewed by the authors and participants in these symposia. It is based on

current knowledge from basic/clinical research and clinical experience. Undoubtedly, the state of the art will improve. A better understanding of the physiological and neurochemical changes associated with opiate addiction will be particularly helpful in producing such improvement. The tremendous interest in endogenous ligands and opiate receptors provides hope that such new information will be forthcoming shortly. Studies of opiate addicts continue to suggest that this disorder is an ideal paradigm for appreciating the importance of biological, psychological, and social factors in the onset and course of the disorder, and its response to treatment. Methadone maintenance has, thus far, proved to be the most effective biological tool available to the clinician for the modification of addictive behavior. It has offered many addicts an opportunity to begin their psychosocial rehabilitation.

James R. Cooper, M.D.
Editor

PART I

METHADONE MAINTENANCE AND DETOXIFICATION TREATMENT

CHAPTER 1. USES OF NALOXONE IN THE DIAGNOSIS AND TREATMENT OF HEROIN ADDICTION

Barbara A. Judson and Avram Goldstein, M.D.

INTRODUCTION

That an opiate antagonist can precipitate an abstinence syndrome in an opiate-dependent subject was first demonstrated in 1953 by Wikler and his colleagues using nalorphine. They demonstrated these two important quantitative relationships: the higher the chronic dosage of morphine to which a subject is addicted, the more intense is the withdrawal syndrome for a given dose of antagonist; and, the higher the chronic dosage of morphine, the less antagonist is required to precipitate a withdrawal syndrome of a given intensity. On the basis of these findings a "Nalline test" was adopted in several states to determine opiate dependence during parole or probation for opiate-related crimes (Elliott 1971).

This test, which was based on change in pupil size, was reliable in identifying people who were dependent on opiates, but much less reliable in picking up occasional users. For exaddicts not currently using opiates, the agonist properties of nalorphine carried the danger of causing either a euphoric reaction that could promote relapse to opiate use, or, more likely, a dysphoric reaction (Fink 1971).

In 1961 Blumberg et al. described a new opiate antagonist, naloxone (Narcan). Their study and the early clinical reports by Foldes et al. (1963) on surgical patients, and by Jasinski et al. (1967) on the pharmacology and abuse potential, showed that naloxone was an almost pure antagonist (i.e., had no significant opiate-like agonist effects), virtually indistinguishable from a placebo.

Unfortunately, from a maintenance treatment point of view, naloxone was found to have a half-life of only about 90 minutes (Fishman et al. 1973), so that large doses (2-3 g) were required to block the effects of heroin use for a 24-hour period (Meyer et al. 1976; Zaks et al. 1971).

Animal experiments such as those by Way and Loh (1976) and Cheney et al. (1972) provided rigorous evidence concerning the quantitative relationship between the degree of opiate dependence and the naloxone-precipitated withdrawal signs, viz., the greater the dependence, the less naloxone is needed to cause a certain intensity of withdrawal syndrome. Each dose of morphine causes a certain quantum of the biochemical adaptive change we call "dependence." This abnormal state dissipates at its own characteristic rate, which is slower than the rate of metabolic removal of morphine from the body. The degree of dependence resulting from a dose of morphine declines, but if the next dose follows while any residual dependence remains from the previous dose, a higher degree of dependence results than before. Eventually, a fluctuating steady state is attained when the degree of dependence caused by each dose exactly replenishes the decay since the previous dose. Thus, the dependence declines somewhat during each interval between doses, and rises again just after each dose. The average level becomes higher (more intense dependence) if the morphine dosage is increased or the interval between doses is shortened, and lower if the dosage is decreased or the interval prolonged. Why, exactly, precipitated withdrawal should require a smaller dose of naloxone the higher the level of dependence is still not entirely clear, but it is a very well established fact.

Naloxone Test for Applicants to Surrogate Opiate Treatment

Blachly was the first to suggest using naloxone to screen applicants for surrogate opiate treatment. In 1973, in an elegant paper that clearly articulated the issues, he described a specific test procedure. Naloxone was given intramuscularly (i.m.) 0.16 mg, and signs and symptoms were recorded after 20-30 minutes. If gooseflesh was not observed, an additional 0.24 mg was given intravenously (i.v.), and observations were recorded again after 15 minutes. He concluded that mydriasis combined with gooseflesh over both upper arms and thorax and sweating were the most definitive signs of a positive test. Of the 32 applicants for methadone maintenance screened by this method, 11 were found not to respond to either the i.m. or i.v. test dose. Blachly pointed out the implication of this finding: without some reliable test for opiate dependence, there is a significant risk of turning pseudo-addicts into real addicts, *de novo*, with methadone.

The next published report of a naloxone test was that of Wang et al. (1974). Patients were given naloxone or saline under double-blind conditions. Signs and symptoms were recorded every 10 minutes for the first 30 minutes, and time of onset was weighed along with severity. While subjective "withdrawal symptoms" were present after both naloxone and saline, withdrawal signs were seen only after naloxone. Thus, the importance of objective signs was highlighted. Another finding of importance was that although all subjects received the same dose of naloxone (0.8 mg i.m.), there was a very great range in the severity of withdrawal effects; in some cases they were so severe as to require 15 mg morphine injections to alleviate them.

A later report by Wang's group (Weisen et al. 1977) dealt with results of 363 naloxone tests. Applicants for methadone maintenance were given 0.8 mg naloxone i.m., then this dose was repeated if there was no response. A smaller dose (0.4 mg) was given to subjects judged to have a "reliable history" of heavy opiate use. After the naloxone test, oral or i.m. methadone was given as required, in repeated doses over a 4-hour period, until all signs of withdrawal were abolished. Most of the subjects (73 percent) received 0.8 mg naloxone, and for these there was a significant ($P < 0.01$) positive correlation between the naloxone test score and the dose of methadone required to alleviate withdrawal signs. Of the 19 applicants given only 0.4 mg naloxone (i.e., who should have had, by history, the most intense precipitated withdrawal signs), 78 percent required more than 40 mg methadone on the first day to alleviate withdrawal phenomena. Among the 59 applicants who had such low naloxone test scores that they received 1.6 mg naloxone during the test, there was no clear relationship between naloxone test score and methadone dose required. Although the experimental design leaves much to be desired, these data as a whole constitute evidence of a relationship between the naloxone test score and degree of opiate dependence.

O'Brien (1976) noted that 15 percent of 40 consecutive applicants to a Philadelphia Veterans' Administration Hospital methadone program had no response to a naloxone challenge, although they appeared to meet all other eligibility requirements. In this study the initial dose was 0.4 mg i.v., followed by additional 0.4 mg injections if the reaction was negative or doubtful, up to a total of 1.2 mg. Withdrawal signs and symptoms in those with a positive response began between 10 seconds and 3 minutes

after injection, and peaked in 15-20 minutes. In a later study, O'Brien et al. (1978) constructed a dose-response curve for precipitated withdrawal by giving a range of test injections of naloxone to methadone patients stabilized at known doses of methadone. They found that as little as 0.1 mg per 70 kg, i.v., produced a prompt withdrawal reaction when the daily methadone dosage was as low as 25 mg.

Zilm and Sellers (1978) gave naloxone tests to eight applicants randomly chosen from those applying to a methadone maintenance program. Injections were made through an indwelling venous catheter, screened from the subject's vision. First saline was given, then naloxone, 0.2, 0.4, and 0.6 mg at 10-minute intervals, but injections were stopped if severe withdrawal effects occurred. In addition to the usual signs and symptoms recorded, the authors also measured heart rate, trapezius electromyogram (EMG), hand tremor, skin temperature, respiratory rate, and blood pressure. All subjects showed dose-related increases in severity of withdrawal signs, the most sensitive indicators being hand tremor, tachycardia, and increased activity in the EMG. No signs or symptoms were observed after the saline injections. The severity of signs noted after the 0.4 mg naloxone dose (but not after the 0.2 mg dose) correlated well with the final score based on all three injections (1.2 mg total). The authors recommend that dependence be determined routinely by giving first saline, then naloxone, 0.2 mg and 0.4 mg i.v., scoring only hand tremor, trapezius EMG, and heart rate.

Judson et al. (1980) gave naloxone tests to 296 applicants for LAAM (levo-alpha-acetylmethadol, levomethadyl acetate) treatment and to 35 of these same subjects later, when they were applying for naltrexone treatment after detoxification from LAAM. The procedure was much like Blachly's. Naloxone (0.02 mg) was first given intradermally to test for allergic sensitivity (none was ever found). Then, after 10 minutes, 0.18 mg naloxone was given i.m. (deltoid), and oral temperature, pulse, and withdrawal signs and symptoms were recorded 20 minutes later. If, in the physician's opinion, clear withdrawal signs (usually gooseflesh over upper arms and thorax, but sometimes heavy sweating or vomiting) were present, the test terminated; otherwise, 0.18 mg was injected i.v., and signs and symptoms were recorded again 5 minutes later. Of the 296 applicants, 60 percent showed a clear withdrawal reaction after the i.m. injection, and another 37

percent after the i.v. injection, but nine applicants showed no effects at all.

Cluster analysis revealed several distinctive modes of response to naloxone. One major cluster included rhinorrhea, lacrimation, yawning, and sneezing; another included shivering, gooseflesh, mydriasis, and chills; a third cluster included nausea, vomiting, and abdominal cramps. The least readily feigned sign was taken from each cluster, and with the addition of sweating (which did not fall into one of the three main clusters), a best set of objective indicators of a positive withdrawal reaction was defined. Thus, the study recommended that an applicant showing one or more of the following signs to a moderate or severe degree -- gooseflesh, rhinorrhea, sweating, or vomiting -- be classified as opiate-dependent for the purposes of admission to surrogate opiate treatment.

The study also examined urine test results taken on the same day for those applicants with clearly positive naloxone tests. Fourteen percent of these did not have an opiate in the urine. On pharmacologic grounds (see above), a negative urine test indicates there was no use of opiates for a couple of days, but does not exclude residual opiate dependence. Conversely, a positive urine test unquestionably means that an opiate has been used recently, but connotes nothing about the state of dependence.

Naloxone Test for Applicants to Antagonist Treatment

The purpose of a naloxone test on applicants for surrogate opiate maintenance is to screen out those who show no evidence of opiate dependence, in order to avoid creating such dependence de novo; it seems axiomatic that pseudo-addicts should be assigned to drug-free treatment modalities.

The naloxone test has a different purpose with applicants for maintenance on an antagonist such as naltrexone. Here it is important to validate the absence of dependence in order to avoid precipitated withdrawal at the first oral dose of antagonist. Various test doses have been used, from 0.4 mg to 1.2 mg i.v. (O'Brien et al. 1978; Tennant et al. 1975/76; Resnick et al. 1974; Hollister et al. 1977; Volavka et al. 1976; O'Brien et al. 1975). Unfortunately, there is no persuasive evidence that absence of withdrawal signs after some particular i.v. test dose of

naloxone necessarily guarantees the absence of discomfort later after the first oral naltrexone dose. Since naltrexone is even more potent than naloxone, and since even a "small" starting dose (e.g., 10 mg) by mouth establishes a very high local concentration of antagonist in the gastrointestinal tract, the predictive value of a negative naloxone test in this context may be unavoidably poor in some subjects. Thus, we observed a few instances in which negative naloxone tests were followed by nausea, cramps, sweating, and gooseflesh after an initial naltrexone dose of 30 mg by mouth. And O'Brien et al. (1978) reported that a starting dose of 10 mg naltrexone sometimes precipitated a mild withdrawal syndrome even after a negative test with 0.8 mg naloxone i.v.

Naloxone for Accelerated Detoxification

Quite apart from its use in testing, naloxone may have a role in facilitating transition from an opiate-dependent state to maintenance with an antagonist such as naltrexone. Precipitated withdrawal appears to represent an accelerated and intensified form of spontaneous withdrawal, i.e., a termination of the state of dependence. Curiously, rigorous proof that an antagonist actually shortens the duration of the dependent state is lacking in animal experiments, but as a practical matter naloxone effectively does this in people. In 1975, Blachly et al. used repeated injections of naloxone to achieve fast detoxification both in heroin addicts and methadone patients. Subjects were admitted to an inpatient unit about 1 day after their last dose of opiate, and were generally discharged 24 hours later. Increasing doses of naloxone were given, i.v., starting with 0.08 mg; incrementation was determined by subject's response to the previous dose.

Resnick et al. (1977) described both a 48-hour and a 24-hour procedure for rapid detoxification prior to administering naltrexone. In the 24-hour procedure, the subject was admitted to the inpatient unit after 1 to 3 opiate-free days. Naloxone was given (1.2 mg i.m. every 30 minutes) until two consecutive injections produced little or no effect. Two large doses of naloxone (100 mg) were then given by mouth, together with 1.2 mg naloxone i.m., 1 hour apart. Finally, naloxone was discontinued, and increasing doses of naltrexone were given hourly, starting with 5 mg, until a total of 50 mg had been given. This type of accelerated detoxification is based upon the assumption, said to be supported by subjects'

statements, that addicts prefer a rapid detoxification with considerable discomfort ("Resnick's flush") to a prolonged one with less discomfort (Resnick et al. 1977; Resnick et al. 1975).

Kurland and McCabe (1976) reported a similar inpatient study, in which various doses of naloxone were given over a 2-day period. Subjects received either two or three injections (mean 3.5 hours between first and second, 24 hours between second and third). In some cases the first injection was followed by two 500 mg oral doses of naloxone 4 hours apart. The duration and amount of prior opiate use by these parolees was apparently less than by Resnick's subjects, and all of Kurland's subjects showed no withdrawal reaction by the third injection of naloxone.

Riordan and Kleber (1980) have combined clonidine and naloxone in a 3-day inpatient procedure. (For reviews on the use of clonidine, see Kleber et al. (1980) and Washton and Resnick (1981).) On day 1, only clonidine was given (6 μg/kg t.i.d.), after a pretreatment dose of 0.1 μg to assess the patient's reaction to the drug. On day 2, 11 μg/kg clonidine was given t.i.d. with 0.4 mg naloxone i.m. every 2 hours for six doses, starting 30 minutes after the first clonidine dose. On day 3, 0.6 μg/kg clonidine was given twice (8 a.m., 2 p.m.), with naloxone (0.8 mg) given every 2 hours. On day 4, clonidine was discontinued, and 1.2 mg naloxone i.m. was given at 8 p.m. If this injection produced no withdrawal signs or symptoms, naltrexone was started at once. In this procedure, clonidine is used to abolish or minimize withdrawal symptoms produced by the early doses of naloxone, so that the entire process of accelerated withdrawal can be completed without the usual array of symptomatology. If the favorable early results are borne out by later and wider experience, this approach will probably be of general value; however, lofexidine may prove superior to clonidine (Washton et al. 1981; Gold et al. 1981).

SUMMARY

Testing for opiate dependence by naloxone administration is a safe and effective technique. With applicants to surrogate opiate maintenance, one wishes to confirm that they are truly dependent on an opiate in order to exclude those who are not dependent. The criteria for inclusion or exclusion are necessarily arbitrary, except that in an individual who has not used opiates at all, no dose of naloxone whatsoever will elicit any withdrawal signs.

We favor Blachly's procedure of giving two injections of naloxone. The first, a small dose i.m., serves to categorize those with a high degree of dependence, who can then be spared the discomfort of challenge with the i.v. dose. For those who do not react to the first dose, the same or a higher dose i.v. should suffice. In Blachly's procedure the high dose is 0.24 mg i.v.; in ours it is similar (0.18 mg i.v.). Naloxone doses 50-100 times higher have been given i.v. to nonaddict volunteer subjects for other purposes (Grevert and Goldstein 1978; Volavka et al. 1979) without effect (indistinguishable from saline). To rule out opiate dependence completely might require much higher doses than have ever been used in a naloxone test. For all practical purposes, however, a degree of dependence so low that 0.18 mg naloxone i.v. elicits no significant withdrawal signs is tantamount to a nondependent state.

Our investigation was unique in carrying out naloxone tests under identical conditions on a group of 35 subjects at two different times in their careers as addicts: initially, when they were dependent on heroin and applying for LAAM maintenance; and finally, many months later, when they had detoxified from LAAM and were applying for admission to a naltrexone program. That the naloxone test changed dramatically, from positive to negative, in the same subjects under the two circumstances, proves conclusively that the test is sensitive to the state of opiate dependence, not merely subject to a large between-persons variance.

With applicants to a narcotic antagonist program one needs to discover and eliminate those who are opiate dependent, without causing them undue discomfort. One also needs to ensure that the first dose of naltrexone will not precipitate a withdrawal syndrome, an event that would certainly be countertherapeutic in a treatment modality requiring

maximal motivation on the part of the patient. What to do about applicants who respond minimally but positively to the naloxone test remains a question. Is it better to start them on naltrexone, risking an adverse reaction? Or is it better to ask them to return another day, hoping they can refrain from heroin use until then?

In our opinion, the naloxone test is an effective tool that should be used routinely for all applicants to surrogate opiate maintenance or antagonist maintenance. We emphasize that in our experience with hundreds of such tests conducted by the two-stage procedure originated by Blachly and developed by us, we have never observed a degree of discomfort that would cast doubt upon the propriety of the test. Against minor discomfort one has to weigh the very serious risk of placing a nondependent person on methadone or LAAM maintenance, and the serious discomfort and countertherapeutic effect of administering a starting dose of an antagonist to an opiate-dependent person.

The use of repeated injections of naloxone to accelerate the withdrawal process prior to starting naltrexone (either with or without added clonidine or lofexidine) is undoubtedly useful for some people. The major drawback is that in the studies done to date, 2-4 days in an inpatient facility have been required, a procedure that is both expensive and impractical for many. Riordan and Kleber (1980) attempted a pilot study of the naloxone plus clonidine withdrawal method on an outpatient basis, but this required that the patients remain in the clinic all day for 3 days. Even though no objective signs were noted, all three subjects dropped out of treatment. Unless the procedure can be done within a 1-day period, the problem of compliance is likely to make outpatient precipitated withdrawal an ineffective way of initiating antagonist treatment.

Acknowledgments

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CRITIQUE

Richard Resnick, M.D.

Judson and Goldstein have presented a clear and comprehensive review of the use of naloxone for diagnosis and treatment of opioid dependence. There are two circumstances in which naloxone is indicated for making a diagnosis of physical dependence on opioids: 1) to screen an applicant's appropriateness for receiving methadone, either for maintenance or detoxification treatment; and 2) to screen recently detoxified individuals for readiness to start treatment with naltrexone. As a treatment in itself, naloxone has been used to precipitate withdrawal and to speed up the detoxification process in preparation for starting naltrexone treatment.

The primary purpose of the naloxone test before methadone treatment is to prevent iatrogenic addiction in someone who is not already physically dependent on opioids. The authors cite two reports in which there was a small percentage of applicants for opioid maintenance (methadone or LAAM) who were found to be not physically dependent on opioids, as indicated by the absence of a withdrawal response to naloxone challenge. These individuals were accordingly refused methadone or LAAM, but it is not stated whether alternative treatments were offered to these non-dependent opioid users. It would be of interest to know, for example, whether these individuals subsequently continued or escalated their use of opioids to the point of developing physical dependence. If so, it may have been preferable to place them on methadone from the start, because of the high degree of psychological dependence despite the absence of physical dependence.

Apparently, there are individuals who use heroin chronically without becoming physically dependent, but nevertheless are unable to remain abstinent. They may have a need for the psychotropic effects of opioids and, therefore, either refuse, or have already failed at, drug-free or naltrexone treatment. It is of interest to know whether the applicants for maintenance who did not have precipitated withdrawal by naloxone were aware of naltrexone as a treatment option at the time they requested methadone or LAAM. Was naltrexone or other treatment services offered to these individuals and, if so, what was their response?

The above considerations are concerned with whether physical dependence should or should not be a mandatory criterion for acceptance into maintenance treatment. I agree with Judson and Goldstein that the use of naloxone for making the diagnosis of physical dependence on opioids is effective, safe, and reliable. For this reason, it can be used as a screening test for physical dependence prior to beginning naltrexone treatment. Since 1973, we have used intravenous naloxone to test readiness to start naltrexone in over 500 individuals. We began using 0.4 mg naloxone intravenously and over the years have gradually increased the dose, noting that some individuals have a precipitated withdrawal reaction to the first dose of oral naltrexone despite a prior negative response to intravenous naloxone. Precipitated withdrawal from naltrexone occurred less frequently as we increased the naloxone test dose from 0.4 mg to 2.0 mg. For the past 2 years we have been using 2.0 mg naloxone IV and, in more than 200 naloxone challenges, only one individual exhibited a clear-cut precipitated withdrawal reaction to 50 mg naltrexone after having no response to the 2.0 mg test dose of naloxone.

Judson and Goldstein note that the most common reactions to naltrexone when it precipitates withdrawal are gastrointestinal symptoms. These are also the most severe and disturbing to patients. We learned early on that a report of minor or transient "queasiness" in the stomach following a naloxone test dose should be regarded as a positive response that contraindicates administration of naltrexone. A gastrointestinal reaction to naloxone of very mild intensity has been followed by severe gastrointestinal pain after oral naltrexone. This reaction probably occurs because the naltrexone acts directly on gastrointestinal receptors which may still be mildly dependent.

Judson and Goldstein pose the question, "Is it better to start naltrexone in patients with a minimal reaction to naloxone despite the risk of precipitating withdrawal, or to have the patient return another day, hoping that they will refrain from heroin use in the meantime?" The answer depends upon the particular patient and circumstances. When the patient is at minimal risk for opiate use, it is preferable to postpone starting naltrexone. When there is a high risk of opiate use, the precipitated withdrawal procedure using repeated naloxone injections can be used to ready the patient for naltrexone immediately. When naloxone was used in this way in our inpatient detoxification ward, the procedure was surprisingly popular. Patients often requested the "flush" and would choose this

method of withdrawal in preference to gradual methadone dose reduction. The reason for this preference is analogous to the way we prefer having adhesive tape removed from our skin: you can remove it slowly and experience a small amount of pain for a longer time, or you can rip it off quickly and experience intense pain for only a few seconds. Most people prefer the latter method.

When our inpatient facility was no longer available, we continued to use naloxone detoxification successfully on an outpatient basis in selected patients with low levels of opioid dependence. However, this procedure can be impractical and time consuming in an outpatient setting because it requires the patient to remain in the clinic for at least several hours under fairly continuous staff observation. There is the possibility that induction onto naltrexone may not be accomplished before the clinic closes at the end of the day. Judson and Goldstein did not mention our use of ancillary medication in the "flush" procedure. Patients were routinely medicated with 1 cc 1/1000 atropine subcutaneously before the naloxone injections, to prevent severe gastrointestinal cramps and pain. Administration of intramuscular diazepam was also helpful in relieving anxiety and restlessness. Since developing the use of clonidine for outpatient detoxification, we have found that the naloxone procedure is rarely needed.

In summary, naloxone has been shown to be useful in diagnosing physical dependence on opioids prior to methadone or naltrexone and in speeding up opioid detoxification in preparation for starting naltrexone. Whenever there is the possibility that naltrexone might precipitate withdrawal, a test dose of parenteral naloxone should be administered beforehand. It is difficult for me to offer a recommendation at this time on the routine use of naloxone for screening applicants for methadone treatment, primarily because of the lack of follow-up information on applicants for methadone who were found to be not physically dependent.

DISCUSSION SUMMARY

James R. Cooper, M.D., Fred Altman, Ph.D., and Kim Keeley, M.D.

There was consensus that a positive response to a naloxone challenge establishes opiate dependence. However, not everyone agreed that a negative challenge ruled out opiate dependence. Some mechanisms were mentioned by which this could occur, e.g., naloxone may not antagonize all opiate receptors and, thus, not produce withdrawal in individuals whose unchallenged receptors remain opiate dependent.

There was further disagreement as to whether a negative naloxone challenge should preclude admission to methadone maintenance treatment. Dr. Goldstein and Dr. Klein were of the opinion that all first admissions to methadone maintenance should be screened for current physiologic dependence using naloxone challenge, and those that display a negative response should be precluded from treatment. However, a number of reasons were presented why a positive response to naloxone challenge should not be required for all first admissions to methadone maintenance. Dr. Senay gave an example of a patient dependent on pentazocine admitted to methadone maintenance treatment who probably would not have responded to naloxone challenge. He postulated that naloxone may not antagonize all opiate receptors equally. Dr. Kreek opposed using naloxone in all clinics because of the unnecessary discomfort suffered by those who are opiate dependent and the associated program costs. She did not believe that these costs were justified to screen out the few patients who are not narcotic dependent at admission when appropriate histories are taken and physical examinations performed.

Some believed that physical dependence is not the exclusive determinant of narcotic addiction. Other factors, including psychological dependence and a compulsive drug-seeking lifestyle were equally important. Dr. Resnick described a daily user of a short-acting narcotic who had not developed opiate tolerance or dependence but did exhibit the drug-seeking lifestyle that he believed warranted admission to methadone maintenance treatment, since attempts to alter this pattern of behavior by means other than methadone maintenance had been unsuccessful.

Naloxone was considered an appropriate preinduction technique for naltrexone treatment. Such use reduces the number of patients whose first naltrexone experience is unpleasant. However, some patients still have symptoms of gastrointestinal discomfort with naltrexone after a negative response to naloxone, probably because the naltrexone can act directly on gastrointestinal opiate receptors which may still be mildly dependent, as observed by Dr. Kreek in her early studies on the effects of orally administered naloxone on methadone dependent patients.[1] Other withdrawal signs are occasionally seen because of the greater antagonistic properties of naltrexone.

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[1]Kreek, M.J. Plasma and urine levels of methadone. NY State J Med 23:2773-2777, 1973.

CHAPTER 2. METHADONE DOSAGE AND DURATION FOR MAINTENANCE TREATMENT

William A. Hargreaves, Ph.D.

This topic bears on two ongoing policy issues engaged by Federal and State government regarding methadone maintenance: Should there be regulatory constraints on the dose of methadone that is allowed, and at what dose level? Should a time limit be put on the duration of maintenance treatment after which a patient would be required to detoxify?

These would not have arisen as regulatory issues were methadone maintenance viewed by everyone as simply another medical or psychiatric treatment. Its explicit role as a part of public policy for controlling crime and related deviant behavior generates counter-pressures in the political arena, sometimes weakly echoed in the academic literature of sociology and political science (Weppner 1979; Smith and Kronick 1979). As clinicians it is our natural response to protect our individual professional decision-making authority by resisting government regulation of clinical practice. Nevertheless, we work in this context of public advocacy and accountability, and are attempting in these reviews to look critically and thoughtfully at the scientific evidence we have so far been able to accumulate about the effects of various policy alternatives.

I have interpreted my task as a reviewer rather narrowly. I have first asked: what evidence do we have that various maintenance dose practices are more effective than others? That quickly became two specific questions: are doses as high as 100 mg/day ever necessary; and, are doses at the low end of common practice, like 30 mg/day, likely to be ineffective for an important group of patients? We do have some evidence on these questions, and I think we can take stock of where we stand and what next we need to know. I then examined what we know about the effects of varying lengths of maintenance on outcome. I found the

evidence in that area more sparsely developed, and the gap between evidence and policy considerably wider.

In reviewing the current status of scientific evidence, I have largely ignored the historical context of these studies. In the original trials of methadone maintenance, Dole and Nyswander (1965; 1967) employed dosages that were generally at or above 100 mg/day. Many of the investigations published in the early 1970s suggested that lower dosage could be employed for most patients. That position has been generally accepted by clinicians. Therefore in reviewing these early studies I have focused on the specific issues that seem salient now, after almost 20 years of experience in the United States with maintenance treatment.

RELEVANCE AND INTERPRETABILITY OF RESEARCH REPORTS

The literature on the topics covered in this review varies greatly in quality, and many studies do not add any usable information in spite of the investigator's attempt to do so. In reviewing papers in order to make a judgment about their relevance, I examined the aspects of study quality that are listed in table 1.

I will illustrate the importance of each of these aspects of study quality as they applied to the review of maintenance dose. The comparisons offered by studies varied greatly. One study might have compared 50 mg/day to 100 mg/day, while the next focused on some entirely different set of alternatives. More troublesome, one study might have all subjects on fixed doses of 50 vs 100 mg, while another study may have attempted the same comparison but have in fact given subjects in each group one of a range of high or low doses so that there was some overlap in actual doses between the two comparison groups. In this case the average dose difference may have been quite small, so that one would be less likely to detect any real difference in dose effect that may exist.

Studies also varied in their endpoints, or outcome measures, although in the case of maintenance dose there is reasonably good concentration on measures of program retention and opiate abuse, and to a lesser extent employment and arrest rate. Study design rarely utilized random assignment of patients to comparison groups, and when this

Table 1. Study characteristics considered in judging design relevance

Characteristic	Definition
Comparison	List or range of values of the independent variable under review.
Endpoints	Major dependent variables.
Design	Randomized, intact groups, time series, correlational, descriptive (single group), or case study.
Sample size	Number contributing information to a finding. A range means fewer Ss were available for some important finding.
Blind conditions	Double blind, single blind, or open.
Time	Time in weeks during which the independent variable was applied or able to have an effect.
Subjects	Special characteristics that limit generalizability.
Group match	Equality of subject groups at baseline, a check on the success of randomization, or the plausibility of a quasi-experimental comparison.
Attrition	Percentage loss of a type that raises the possibility of biased attrition.
Biased loss	Data on types of subjects lost to outcome measurement.
Confounding	Plausible alternative explanations not excluded by data analyses or otherwise addressed, rated probable, possible, or no (reviewer saw no plausible possibilities).

Table 1--(continued)

Characteristic	Definition
Statistics	Rated excellent, adequate, weak (less than optimal statistical power), vague (inadequately reported), wrong (errors obscure inference), or not reported.
Inference	Summary judgment of the inference level and design relevance to the issue under review, rated as causal (perhaps with reservations), correlational, suggestive, or none (irrelevant to the issue under review, in spite of its title or assertions of relevance by the investigator).

was not done there were usually serious problems of confounding the treatment effect with baseline differences in the subjects. Some other designs can yield useful results, however. Sample size directly affects the statistical power of a study--its ability to detect an effect that is really there. The announced sample size is often not the sample size actually used, however, due to attrition losses, or to the fact that the comparison of interest involved only a subset of the total subjects.

The nature of the blind conditions are particularly important in separating pharmacological effects from expectation effects and from the other psychological aspects of a treatment. Under double blind conditions, neither the subject nor the treatment staff know the subject's treatment assignment. This is partly dealt with in single blind studies, where only the subject is blind, but staff expectations can produce spurious effects when, for example, they are quicker to pull low-dose subjects from the study when the subject seems to be in difficulty. The length of time that subjects are exposed to a treatment comparison is also a factor in study power when treatment effects can be expected to have their impact gradually over a long time. A short time period results in a weak comparison just as would a small treatment contrast (e.g., a 5 mg difference in methadone dose). Studies may also be less relevant if they have a narrow selection of subjects, limiting generalization. In maintenance studies, newly inducted clients may show different effects than clients who have been in treatment already for a year. The group match at baseline is also important, even in randomized trials, since the subject groups may, by chance, be poorly matched in spite of random assignment. This issue is even more important in nonexperimental studies, of course. Attrition of subjects from initially well-matched comparison groups allows group comparability to decay. For example, if one treatment leads to higher dropout than another, the ability to interpret differences among the survivors may be compromised. One can check for this by analyzing whether a biased loss has occurred by comparing the baseline characteristics of the survivors in each treatment group. When attrition has been large, failure to specify whether the attrition resulted in biased losses is a weakness in research reports. All of these problems may result in confounding of other factors with the intended treatment comparison. The risk of confounding is often not recognized by inexperienced investigators, or if recognized is not discussed frankly in research reports, so

the reviewer must consider the possible sources of confounding, and determine whether they can reasonably be ruled out on the basis of the information presented by the investigator. Statistics, the application of methods of inference to the data gathered in a study, is a highly technical and often very time-consuming undertaking that, when poorly done, can limit the usefulness of an otherwise excellent study. Sometimes the data are not summarized in a way that allows one to draw any conclusion at all. In other cases the individual statistical procedures are correct but the overall data analysis strategy seriously weakens the power of the study.

All of the foregoing factors contribute to the clarity, power, and relevance of a study, and I have summarized my judgment about these factors in the final item in table 1, the level of inference. If the study is to be really useful, one usually needs to be able to make a causal inference--to conclude that the treatment difference caused or did not cause some effect. The conclusion that there is no effect is the most demanding conclusion, and requires the best conditions of study power. When a causal inference is not possible, one may still learn something from studies which imply a correlational association or lack of association. Such studies can sometimes rule out certain effects, or effects larger than a certain size. Studies that do not allow even this level of inference may nevertheless be suggestive of certain hypotheses. Unfortunately, many of the studies reviewed here allow no inference at all, in spite of the investigator's claims to the contrary.

PHARMACOLOGICAL EFFECTS OF DOSAGE LEVEL

We are concerned with the differences in treatment effectiveness that reflect pharmacological effects of different dose regimens, rather than the expectation effects, the patient-staff interaction related to choice of dose, or other interpersonal or psychological aspects of treatment that may be related to dose level. The use of double-blind controls, of course, is the most helpful design feature in allowing us to distinguish pharmacological from other effects of different dose levels.

Table 2 lists 23 reported studies that were asserted by their authors to be relevant to the effects of dose, either as the primary focus of the study or as an incidental finding. The studies are listed in what I judge to be the order of their clarity and importance as evidence about the narrower issue of pharmacological effects. The strongest studies should set the major conclusions or propositions, and then the weaker studies can be reviewed to see whether they contradict the stronger evidence. The first few studies are the only ones that directly provide any relevant evidence. Another six or eight are indirectly relevant. The remaining studies are so limited or tangential that they could hardly influence the overall conclusions, but are included because they claim some relevance, and therefore seem to deserve a statement about the reasons for their being set aside.

Review of Studies

Ling, Charuvastra, Kaim, and Klett (1976). Ling et al. report a randomized, double blind comparison of l-alpha-acetylmethadol (LAAM) and two dose levels of methadone in the initial maintenance of 430 street addicts. This was a collaborative study carried out in 12 Veterans Administration hospitals. The two methadone groups are of primary relevance here. Both groups received 30 mg/day the entire first week, and were incremented 10 mg/week until they reached a maintenance dose of either 50 mg/day or 100 mg/day. Subjects were continued on this fixed dose until they had been in maintenance for 40 weeks, providing a 33-week exposure to the full dose difference.

The principal endpoints were retention in treatment and opiate abuse rate, based on urine test results during treatment. In addition, this study included weekly self-reports of symptoms, an analysis of reasons for termination, extensive collection of routine clinical laboratory data for evaluation of safety, and a global rating of degree of improvement made by staff at 40 weeks or at early termination.

The approach to the data analysis was exemplary, under the direction of Dr. Klett at the data coordinating center for the study. Especially important methodologically was the skillful treatment of urine test data, since such data have been handled badly in most other studies. An index of illicit morphine use was constructed, combining in a single number for each subject the information deemed

Table 2a. Design relevance of studies of the pharmacological effects of maintenance dosage on program retention, opiate abuse, and other measures of during-treatment outcome

Reference	Ling et al. 1976	Goldstein, Judson 1973	Garbutt, Goldstein 1972	Jaffe 1970a	Ling et al. 1980	Berry, Kuhn 1973
Comparison	50 mg 100 mg	40 mg 80 mg 160 mg	30 mg 50 mg 100 mg	55-110 mg 30-45 mg	50-60 mg 100 mg	100-50 mg 100 mg
Endpoints	retention opiate abuse global change	retention opiate abuse symptoms	retention opiate abuse symptoms	retention opiate abuse employment	dose change symptoms	retention opiate abuse symptoms
Design	random	random	random	random	intact groups	random
Sample size	200 (221)	103 (66)	180 (27)	126 (54)	49	52
Blind	double	single	double	double	double	double
Time	40 wk	18 wk	53 wk	12 wk	6 wk	20 wk
Subjects	new admission male veterans no pending criminal charges	10 2 wk after admission	new admission	new admission	male veterans 40 wk after admission	stable on 100 mg
Group match	good	good	not reported	good	poor	good
Attrition	23%-40 wk	45%-18 wk	45%-53 wk	46%-14 wk	0	37%-20 wk
Biased loss	ok	not reported	not reported	not reported	na	ok
Confounding	no	possible	no	possible	no	no
Statistics	excellent	vague	wrong	weak	adequate	adequate
Inference	causal	causal	causal	causal	causal	causal

Table 2b. Design relevance of studies of the pharmacological effects of maintenance dosage on program retention, opiate abuse, and other measures of during-treatment outcome

Reference	Stitzer et al. 1979	Goldstein et al. 1975	Siassi et al. 1977a	Havassy et al. 1979; 1981	Goldstein 1970; 1971; 1972b,c	Stitzer et al. 1981
Comparison	5-20 mg raise	increasers vs others in self regulation	<61 mg >79 mg	self regulation incentive standard	30 mg 50 mg 100 mg	20 mg raise
Endpoints	symptoms opiate abuse	dosage opiate abuse	opiate abuse alcoholism	dosage opiate abuse	opiate abuse symptoms	opiate abuse symptoms
Design	time series	correlational	correlational	correlational	intact groups (subset random)	time series
Sample size	23	59	46	70	206	8
Blind	open	open	open	open	single	single
Time	1 day	25 wk	variable	48 wk	variable	6-17 wk
Subjects		established on methadone maintenance	retained >2 yr	established on methadone maintenance	new admission	established on methadone maintenance
Group match	na	na	fair	good	not reported	na
Attrition	0	not reported	not reported	10%-16 wk	not reported	0
Biased loss	na	na	na	na	not reported	na
Confounding	possible	possible	na	possible	possible, except random subset	possible
Statistics	adequate	weak	vague	adequate	not reported	weak
Inference	correlational	correlational	correlational	correlational	suggestive	suggestive

Table 2c. Design relevance of studies of the pharmacological effects of maintenance dosage on program retention, opiate abuse, and other measures of during-treatment outcome

Reference	Jaffe 1970b	Berry 1972	Handal, Lander 1976	Perkins, Bloch 1970	Brown et al. 1972
Comparison	90±30 mg 53±40 mg	30 mg 50 mg 100 mg	< 40 to >100 mg	<81 mg >80 mg	<60 mg >59 mg
Endpoints	retention opiate abuse employmnt	retention opiate abuse	attendance opiate abuse	retention	retention opiate abuse employment arrests
Design	random	correlational	correlational	correlational	correlational
Sample size	126 (54)	200 (110)	155	751	273 (15)
Blind	single	single	open	open	open
Time	10 wk	16 wk	variable	variable	variable
Subjects	new admission	new admission			
Group match	good	poor	na	na	not reported
Attrition	42%-36 wk	45%-16 wk	not reported	not reported	50%
Biased loss	yes	not reported	not reported	not reported	not reported
Confounding	probable	probable	probable	probable	probable
Statistics	wrong	vague	wrong	weak	vague
Inference	suggestive	suggestive	none	none	none

Table 2d. Design relevance of studies of the pharmacological effects of maintenance dosage on program retention, opiate abuse, and other measures of during-treatment outcome (continued)

Reference	Bowling et al. 1973	McGlothlin, Anglin 1981b	Langley et al. 1973	Siassi et al. 1977b	Craig 1980
Comparison	70-80 mg >139 mg	mean 82 mean 93	<19 to >100 mg	<61 mg >79 mg	mean 30 mg
Endpoints	opiate abuse employment arrests	(very compre-hensive)	opiate abuse	retention type of termination	retention opiate abuse employment arrests
Design	correlational	intact groups	correlational	correlational	descriptive
Sample size	131	347	144	86	221
Blind	open	open	open	open	na
Time	variable	variable	variable	variable	na
Subjects	current clients		current clients	terminated clients	new admission
Group match	poor	fair	not reported	poor	na
Attrition	not reported	9%	not reported	not reported	90%-52 wk
Biased loss	not reported	na	not reported	na	na
Confounding	probable	possible	probable	possible	na
Statistics	vague	excellent	wrong	adequate	na
Inference	none	none	none	none	none

relevant to this aspect of treatment outcome. Recent test positives were weighted more heavily than early test positives, so that a subject who showed progressively less opiate abuse would be assigned a lower score than a subject with the same proportion of positive tests scattered evenly along the treatment period. Scheduled tests that were missed were neither discarded nor treated as definite positives, but were counted as a fractional positive, using the fraction of all urine tests in the study that were positive. I understand that in subsequent studies this procedure was modified to estimate a missed test as a fractional positive using each individual subject's proportion of positive tests (Klett, personal communication, 1981). The use of this index increases the statistical power of the analysis in several ways. Early terminators can be included in the analysis so long as they have a minimum number of tests, which increases the effective sample size. (Ling et al. required that the subject be in the study at least 50 days to be included in this analysis.) All of the information about opiate abuse is included in a single statistical analysis, avoiding the loss in statistical power associated with computing multiple tests of significance. Finally, the index has somewhat better scale properties than a simple proportion, and one can apply the most powerful least-squares statistical tests, such as analysis of variance, with reasonable confidence. By using this index, Ling et al. probably make very efficient use of their available sample, from a statistical point of view.

Table 2 also shows that this study has the largest sample size of any of the good quality studies. Two hundred and eighty-eight Ss were assigned to the methadone groups, although only 221 of these were available for the opiate abuse analysis. However, the presence of the additional group of LAAM subjects in the analysis provides greater statistical power due to the more precise estimate of within-group variability. Therefore this study not only exceeds the power of any of the other available studies for any shared outcome measure, but in the case of urine test evidence of opiate abuse, this study is probably very much more sensitive to a dose effect than any other study. This did not happen by accident. The study was designed, and heavily funded, to be able to demonstrate the lack of difference in safety or efficacy of LAAM compared to methadone. The potency equivalence of LAAM to methadone during chronic dosing was known only approximately when the study was designed. The two dose levels of methadone, at the upper and lower end of the range that

previous reports had suggested was optimal for maintenance, were intended to bracket the methadone dose that was equivalent to 80 mg TIW of LAAM. The design succeeded, in that the LAAM group showed outcomes on most measures that were intermediate between the high and low dose methadone groups.

Statistical significance was found between the 50 and 100 mg methadone groups on the opiate abuse index ($p < .05$), considered by the investigators to be their most important measure of efficacy, and on the global staff rating of improvement ($p < .01$). Statistically significant differences were not reported on measures of retention to 40 weeks (42 percent on 50 mg versus 52 percent on 100 mg), although the analyses were not optimal on this measure, as discussed below. Significant differences were also not reported for individual symptom complaints, although the authors did not report what were probably their most sensitive symptom measures -- three factor-based subscales of overdosing, underdosing, and other somatic symptoms. However, there is available a 100-page expansion of the published paper that provides data and analyses in much greater detail (Klett 1975). In this supplement it is reported that while there was significant reduction in all symptom levels over time, the three treatment groups do not significantly differ at any point. Overdosing symptoms drop most rapidly, showing little change after week 4. Underdosing symptoms are well down by week 8 and show a slight further decline through about week 24. Other Somatic Concern declines more gradually from week 0 to about week 24. Subject attrition complicates the interpretation of these symptom trends. Graphs are presented for two sets of subjects--those surviving in the study to week 24, and those surviving to week 40. Since attrition was 50 percent by week 24 (85 percent of the eventual 40-week attrition), these symptom figures and tests of significance omit most of the subjects who may have dropped because they were experiencing greater than average symptom distress. An analysis of subjects surviving to week 4 might have been informative. No details were reported on the analyses of arrests, employment, or income, either in the published report or the supplement.

Interpretation of this study requires us to consider for a moment the logic of proving that two treatments are equivalent. If a study of good design but limited statistical power finds a significant difference in treatment effectiveness, we are impressed that we have some new knowledge. What if it fails to find a significant difference?

We are not so easily unimpressed (to borrow a felicitous remark from Yeaton and Sechrest (1981)). One approach to arguing the equivalence of two treatments is to use the logic of statistical estimation. The confidence interval allows us to make a statement like, "We are 95 percent confident that the true difference between these treatments is not greater than such-and-so." In fact, if a study does find significant differences on at least some of the outcomes, it may give us greater confidence that the sensitivity of the study has not been destroyed by some unrecognized problem. The issue is not whether a significant difference is found, but how small an upper bound can be put on the size of the difference. A study that finds a significant difference may nevertheless put a smaller upper bound on the difference than a study of poor power that does not detect a significant difference. Unfortunately, none of the investigations reviewed here present interval estimates even when arguing for equal efficacy of two treatments, so we will have to construct them whenever possible. The topic of proving the equivalence of two treatments is discussed in more technical detail by Dunnett and Gent (1977).

Ling et al. do not report interval estimates, but for the opiate abuse index, for which they report group means, sample sizes, and the F value, we can reconstruct, at least approximately, the confidence intervals on the difference between outcomes on 50 mg vs 100 mg. For the urine test index of opiate abuse they report F=6.19 and group means (sample sizes) as follows: 33.3 (110) for 50 mg of methadone; 22.6 (111) for 100 mg of methadone; and 20.8 (96) for 80 mg of LAAM. This allows us to estimate the full F table and generate approximate confidence intervals, as shown in table 3. Even using the stringent 99 percent confidence interval, we estimate that patients on a fixed dose of 50 mg/day will show an opiate abuse index no greater than 11.4 points higher than patients on 100 mg/day of methadone.

How big is this difference? To understand its clinical importance, we need to review the meaning of the opiate abuse index. The index has a range of possible values from 0 (if a patient never has an opiate-positive urine test and never fails to provide a urine sample upon request) to 120 (if a patient is opiate-positive on every test and never fails to provide a urine sample). Recent tests are weighted more heavily--an opiate positive within the most recent 8 weeks counts 5, while one in the preceding 8 weeks counts 4, and so forth. A refused urine test

Table 3. Reconstructed analysis of variance and confidence intervals for the opiate abuse index (from Ling et al. 1976)

Source of variation	df	SS	Mean Square	F
Treatments	2	91.33	45.66	6.19
Error	312	2301.6	7.377	
Total	316	2392.9		

Mean (50 mg methadone) - Mean (100 mg methadone) = 33.3 - 22.6 = 10.7

t(df=312, .975) = 1.96

t(df=312, .995) = 2.60

Pooled estimate of within-group variance = 7.377

Standard error of mean difference = $\sqrt{(7.377)\ (1/110 + 1/111)}$ = .36

95% confidence interval = 10.7 + (1.96) (.36) = 10.0 to 11.4

99% confidence interval = 10.7 + (2.60) (.36) = 9.7 to 11.7

counts 0.22 as much as a positive test--1.1 in the most recent 8 weeks, and so forth. If a patient were in the Ling et al. trial for the entire 40 weeks, never failed to provide a urine sample each week when asked, used opiates steadily during his first 4 weeks on maintenance, but thereafter showed exactly one opiate positive result every 4 weeks, his opiate positive index would be 33, about at the observed mean in the 50 mg group. If instead of six positive tests in the final 24 weeks he had only three (one each 8 weeks), his index would be 12 points lower, more than the maximum difference suggested by the study findings. Is this a clinically important difference? Remember, this is the average difference--it is as if every patient on 100 mg showed that much less opiate abuse than he would were he maintained on 50 mg.

Alternatively, we could assume that most patients would do fine on either dose level, but a few would do much worse if they were on 50 mg rather than 100 mg. Suppose again that all patients remain for 40 weeks, and that the typical patient shows the following number of opiate positives in each of the 10 4-week periods: 4, 3, 3, 2, 1, 1, 0, 0, 0, 0. This would yield an opiate abuse index of 23, the observed mean in the 100 mg group. I would be pleased if all the patients in our program showed this pattern during their first 40 weeks on maintenance.

Now consider the following "worst case" example. Suppose the poorer performance of the 50 mg group were due entirely to the presence of a few people who were continually abusing opiates, so that all tests were positive, except that they refused one test in four. This would give each of them an index of 96.6, 73.6 higher than the "typical" patient. We are confident (well, 99 percent confident) that the true increase in the opiate abuse index on 50 mg maintenance is no more than 11.4, which is equivalent in our example to having 15.5 percent of the patients showing continuous opiate abuse on 50 mg who would be doing fine on 100 mg. We are equally confident that the difference is not less than 9.7, corresponding to an excess of 13.2 percent in such "treatment failures." If we assume that in reality the group difference is not concentrated in a few clear treatment failures, then we must assume that many more than 15 percent of patients show more opiate abuse on 50 mg than they would on 100 mg. I think differences on this order could easily be missed in casual clinical observation. I do not find myself ready to dismiss them as clinically unimportant, but that is a matter for each reader to judge.

Ling et al. do not report any other outcome measures in enough detail for this type of reanalysis except treatment retention. With 146 Ss each at 50 mg and 142 at 100 mg, they found 40-week retention rates of 42 percent and 52 percent, respectively. Their supplemental report shows that this differential rate of attrition occurred only in the first 17 to 20 weeks, however. After 20 weeks the retention was approximately 54 percent and 63 percent on 50 and 100 mg, respectively. They report the difference in 40-week retention as nonsignificant. I presume they did this using the rationale that a two-tailed test was appropriate, since we would make a substantive interpretation even if attrition were higher in the 100 mg group (due to toxicity, for example). However, using a one-tailed test the above difference in attrition is significant ($P < .05$). Furthermore, a more sensitive and appropriate analysis would have employed life table methods that use all of the information about time to dropout for every subject (Dixon and Brown 1977, pp. 741-770). Using the information at hand, one can calculate that the 95 percent confidence interval on the difference between these two proportions is -0.02 +0.22 (Fleiss 1981, p. 29). By this reasoning the Ling et al. findings suggest that we can rule out a difference in 40-week retention rate greater than a difference like 36 percent versus 58 percent.

How large or important is a difference in retention of the size observed in this study? The observed difference corresponds exactly to what Cohen (1977, p. 184) called a "small effect size," where effect size is defined as

$$ES = 2 \left(\arcsin \left(\sqrt{P1}\right) - \arcsin \left(\sqrt{P2}\right) \right) = .20$$

More concretely, among the 13 VA Hospital sites in the Ling et al. study, 40-week retention varied from a low of 18 percent to a high of 77 percent. Individual site retention rates on 50 and 100 mg are shown in table 4, arranged in order of total sample size. Although the sites varied widely in retention in the study, retention was greater on 100 mg than on 50 mg in 7 sites, equal in 3 sites, and lower in only 2 sites, one of which had only 9 subjects. Therefore the differential retention rates are seen in a majority of the individual clinics in spite of the wide variation in overall study retention from clinic to clinic. While this differential retention is consistently seen, its clinical meaning is less clear than the dosage-related differences in opiate abuse, since it is retention in a double blind study, and some of the losses

Table 4. Retention rates at 40 weeks in individual of the VA-SAODAP cooperative study (from Klett 1975)

Site	Total methadone subjects	Retention percentage by dose	
		50 mg	100 mg
A	60	80%	87%
B	40	70	80
C	40	5	10
D	30	27	53
E	27	20	17
F	20	40	60
G	20	30	30
H	20	60	70
I	11	0	40
J	9	25	20
K	6	33	33
L	5	0	0
Total	288	42%	52%

represent patients who left the study but continued in open methadone maintenance. Thus study attrition is a mixture of real treatment attrition plus less serious problems that led the patient to withdraw or be withdrawn from the study.

Goldstein and Judson (1973). This was a well designed randomized single blind trial comparing 40, 80, and 160 mg/day of methadone after an identical 9-week induction period for all subjects onto a stable dose of 80 mg. At the start of week 10, and of each of the next 7 weeks, the high dose group received a 10 mg increase, and the low dose group received a 5 mg decrease, while the middle dose group remained on 80 mg. Each group then continued for 10 weeks on a stable dose, providing an 18-week exposure to the dose differentiation. The study endpoints were program retention, reason for termination, opiate abuse, and a 45-item symptom questionnaire at weeks 1, 9, and 27. All patients came to the clinic twice daily to receive their dose. Since a separately reported aspect of this experiment was a single blind comparison of split dosing with regular dosing, half of the subjects received placebo at their second visit each day (Goldstein 1972a).

One hundred and twenty Ss were randomly assigned at admission, 40 to each group, although 17 of these 120 dropped out before the dose differentiation began. The authors report that the original groups of 40 did not differ significantly on any of 29 background variables, although the data and analyses are not presented. No information is presented on whether the groups remained equivalent on these variables at week 10 when dose differentiation began, or at week 27. Some other data do suggest that the week-27 survivors in the low dose group were different than survivors in the other groups--for example, showing poorer attendance in weeks 3-9.

Study retention, and to a lesser extent program retention, were poorer in the 40 mg group than in the other two. Tests of significance are not reported. Estimating from the figure showing survivorship, it appears that study retention of week 9 survivors at week 27 was 45 percent (15/33) at 40 mg, 71 percent (25/35) at 80 mg, and 74 percent (26/35) at 160 mg, which yields a chi-square with 2 df of 7.34 ($p < .05$). Interpretation of this higher attrition on 40 mg is compromised by the single blind nature of the study, since nurses hearing complaints from patients they knew were on low dose may have been more ready

to pull them from the study. Indeed, part of the difference is accounted for by patients who remained in treatment but left the protocol. A second problem is the poorer attendance during weeks 1-9 among the low dose patients, suggesting that part of the attrition difference may have been a failure of the randomization to equalize the groups. A third puzzle is a possible interaction between dose and dose splitting in their effects on retention. Split versus single daily dosing had no effect on outcome (Goldstein 1972a) except a trend among the 40 mg patients for once-daily patients to show a higher dropout rate than twice-daily patients. Could the twice-daily dispensing have protected 40 mg patients from problems that were experienced by those on the standard once-daily dosing? The authors mention these three issues in discussing the interpretation of the greater attrition on 40 mg, implying that they strengthen the evidence that there is no difference in outcome on 40 mg compared to the higher dose levels. I certainly agree that these problems weaken the evidence that there is a difference in outcome, but it is equally true that they weaken the evidence that there is not a difference. These problems make it difficult to interpret the size of the difference in retention. However, one might argue that it is of interest to estimate the upper bound on the difference in retention between the 40 mg group and the combined 80 mg and 160 mg groups. The observed values are 45 percent (15/33) in the 40 mg group, and 73 percent (51/70) in the combined high dose groups, a difference in retention of 0.28. The 95 percent confidence interval on the population difference is 0.06 to 0.50. Thus the upper bound on the difference suggested by this study (0.50) is considerably larger than the upper bound estimated from the Ling et al. data (0.22). In this sense, the Ling et al. findings provide stronger evidence for the small size of the dose-related difference in retention than do the Goldstein and Judson findings.

Opiate abuse rates reported from this study are very low. By week 9, about 80 percent of all patients showed no opiate positives in the current week (tested on the average of one day in five). Therefore there was very little available variance within which to detect dose-related differences during weeks 10 to 27, the actual period of the study. Furthermore, the authors point out that the groups had probably taken differential attrition by week 9, selectively eliminating opiate-abusing patients, especially from the 40 mg group. Abuse rate was analyzed

week by week rather than aggregated in some way to increase power and deal with the differential attrition, thus wasting most of the available statistical power. A reanalysis of these data using something like the Ling et al. opiate abuse index would allow more powerful parametric statistical analysis and the estimation of an upper bound on the dose-related difference in opiate abuse. The reported rates are very close, but with the smaller sample size (down to 66 by week 27) it is unclear whether the upper bound is likely to be lower than implied by the Ling et al. data.

The final endpoints in this study are the items of the symptom questionnaire at weeks 1, 9, and 27. No tests were made for group differences in change in these symptom reports. Furthermore, individual items, likely to be very unreliable, are analyzed rather than subscale scores of some type. This approach is usually a very weak use of self-report data. In fairness to the authors it should be noted that this criticism applies to most of the studies in this review that use self-report symptom data. In my judgment the symptom data are uninterpretable in the form reported.

Garbutt and Goldstein (1972). This is a randomized single blind trial comparing dose levels of 30, 50, and 100 mg/day for addicts newly inducted onto methadone maintenance. All Ss began at 30 mg on the first day. The 30 mg group was left at this dose. The 50 mg group received 10 mg increments on days 3 and 5. The 100 mg group received 10 mg increments every other day until reaching 100 mg on day 15. One hundred and eighty patients were entered into the trial, but the investigators attempted to follow all of them for only 3 months. They attempted to follow a subset of 120 for 6 months, and a subset of 60 of those for 12 months. The clinic setting was deliberately patterned after the clinic in which the Goldstein and Judson (1973) and Goldstein (1970; 1971; 1972) studies were done, but differed in only dispensing in the evening, being less adequately staffed, and showing poorer general outcomes, the authors assert, than did the other clinic during the period in which the present study was carried out.

Endpoints were similar to the ones used by Goldstein and Judson (1973): retention in treatment, opiate abuse, and self-reported symptoms. Retention and opiate abuse were analyzed only at weeks 13, 27, and 53, with sharply decreasing sample sizes at successive times. Opiate abuse data at week 53 were available on only 27 patients. With

regard to the opiate abuse measure, attrition was 15 percent (27/180) at 13 weeks, 31 percent (37/120) by 27 weeks, and 55 percent (33/60) at week 53. Symptoms were analyzed at weeks 3, 5, 9, 13, 27, and 53, with attrition comparable to that for the opiate abuse measure.

Program retention was analyzed in two ways. The most sensible one counted patients temporarily in county jail but receiving methadone from the program as being active patients. The percentages retained were as follows:

Dose level	30	50	100	N
At 13 weeks	95	98	87	180
At 27 weeks	72	90	75	120
At 53 weeks	60	70	50	60

Keep in mind that these are not the same groups of patients, but rather nested subsets, and the stability of the later figures is much lower. The authors report 50 mg superior to 100 mg at 13 weeks and 50 mg superior to 30 mg at 27 weeks (both $P < .05$). This is presumably based on pairwise chi-square tests, three of them at each time point, an approach that runs considerable risk of capitalizing on chance associations. If an overall chi-square test is done at each time point, it is seen that retention is significantly related to dose only at 13 weeks (chi-square with 2 df is 6.96, $P < .05$), not at 27 weeks (chi-square with 2 df is 4.35, $P < .25$). The 53-week differences do not approach significance, as is correctly reported by the authors.

In examining opiate abuse, Garbutt and Goldstein unfortunately weakened their analysis by discarding all of their urine test data except for the three 4-week periods prior to weeks 13, 27, and 53. These periods were analyzed in two ways. In one analysis all urine tests were pooled within each of the three groups, spuriously increasing power by ignoring the greater dependency among urine tests for the same patient, compared to urine tests from different patients. They report some significant differences favoring the higher doses, but it is impossible to interpret them with the data reported in this way. A second analysis reported the proportion of patients with no opiate positive tests during the 4 weeks. This analysis

showed little difference at 13 weeks, and larger differences at the later times but with such small sample sizes that the differences cannot be interpreted.

Symptom self-reports, as with most of the studies reviewed, were analyzed as single items, eliminating much chance of seeing consistent dose differences, even though most subjects reported changes in many symptoms from the pretreatment baseline. In this study the authors performed statistical tests for dose group differences, but used Wilcoxon tests on simple difference scores, a procedure that overcorrects for baseline level. The few differences found could easily be attributed to chance (eight tests significant at $P < .05$ among 136 between-dose tests, by my count). Most of these tests have such small samples that they lack enough power to mean anything.

This is another study that utilized a randomized single blind design that could yield very useful information about dose effects, especially since it is one of only two studies that examined the 30 mg/day dose, a dose that seems to be in fairly common usage (NIDA Services Research Branch 1979). However, due to the limitations of the study it is not at all clear that the authors were correct in concluding that 30 mg had a poorer result than the higher dose levels, yet clinically important differences in effect cannot be ruled out either.

Are these results inconsistent with the Ling et al. findings? Here are data that show a trend for 100 mg to lead to lower retention than 50 mg, the opposite of the Ling et al. findings. What is the upper bound suggested by these data for the greater program-retention power of 100 mg, as found by Ling et al.? At 13 weeks the 95 percent confidence interval on the superiority of 100 mg is -0.22 to 0.0, at 27 weeks it is -0.34 to 0.03, and at 53 weeks it is -0.40 to 0.0. Therefore these retention data are inconsistent with the Ling et al. findings, and we need to consider the differences in the two studies that might account for this. One difference is Garbutt and Goldstein's rapid induction onto 100 mg within 15 days. If this were causing excess attrition, it should be seen during the first 4 to 6 weeks, but those data are not reported. Another difference is the evening dispensing hours, which is relatively unusual for the maintenance programs in which controlled dose studies have been carried out. It would require an interaction of dose with the time of day of dispensing, such that 100 mg would be particularly disadvantageous to dispense in the evening. We know so

little about the effects of these procedural aspects of maintenance programs, or the diurnal modifications of methadone effects during chronic dosing (much less their interactions), that this possibility is pure speculation. Perhaps others will find differences in the subject population or treatment conditions that could explain the contradictory outcomes, but any explanation will probably not be convincing in the absence of a confirming study. At the moment we are left with a contradictory finding, so that the policy implication we take must be based entirely on the relative general quality of the Ling et al. (1976) study versus this one. In that case this single finding of the Garbutt and Goldstein (1972) study would have to be set aside.

Jaffe (1970a) reports a randomized trial comparing a low dose to a high dose regimen. It appears to have been double blind as far as patients and "program staff" were concerned, although it is unclear whether the prescribing physician was blind. Sixty-three patients newly admitted to maintenance were randomly assigned to standard dose (N = 32) or high dose (N = 31). All Ss were stabilized during the first 2 weeks on a doctor's choice dose which appears to have been 32 mg on the average with a standard deviation of about 8. At the end of weeks 2 to 7 the high dose patients received a 10 mg increase unless side effects occurred. All high dose patients reached 100 mg at week 7 except one who was stabilized at 55 mg due to side effects. The low dose group showed no long-term trend to increase dose, had a mean dose level of 36 mg, and only one patient exceeded 45 mg during the 14 weeks of the study (12 weeks of differentiated doses). Thus during the final 7 weeks of the study the dose levels of the two groups were well differentiated, averaging 36 mg and 100 mg. Endpoints were treatment retention, opiate abuse, and employment. The opiate abuse measure appears to have been based on one to three urine tests per week, although this is not stated. In the clinic where the study was carried out, patients showed high early dropout rate if they were continuing to use opiates, to a degree that exceeded the experience in other Chicago clinics under the direction of Dr. Jaffe at that time. This appears to have been due to a vigorous staff policy of high expectations for patients very early in their treatment.

During the 12-week exposure to these dose regimens there were small trends favoring high dose that generally did not reach statistical significance. Retention at week 14 was 58 percent in the high dose group, 50 percent on low

dose. Opiate abuse showed a trend toward increasing superiority of the 100 mg group during the final 4 weeks of the study, but the statistical tests applied repeatedly, each to only one week's data, represent a weak approach to the analysis, and the single significant difference at week 13 is uninterpretable. The author asserts that opiate abuse is equivalent in the two groups at week 17, but no data beyond week 14 are presented. The number of patients unemployed at the start of treatment who subsequently obtained jobs was greater for the high dose group, but not significantly so.

Interpretation of these results is difficult because of the relatively low power of this study with its small sample sizes, brief exposure to the treatment differences, and very high early attrition. The 95 percent confidence interval on the degree of superior treatment retention on 100 mg is -0.20 to 0.38; thus this study provides much weaker evidence for the equivalence of these two doses than does the Ling et al. study, as regards any effect on treatment retention. The opiate abuse data are not presented in such a way that any very powerful use could be made of them in a reanalysis, especially since the most relevant subjects seem to have been dropped from the study. In the presence of the trends favoring 100 mg on all three endpoints, it hardly seems that this study provides evidence for dose equivalence, any more than it provides evidence for a differential dose effect.

Ling, Blakis, Holmes, Klett, and Carter (1980). At the end of the large VA collaborative study discussed above, the 68 subjects retained at the end of the trial at Sepulveda VA Hospital were entered into a parallel time series design. All Ss were abruptly changed from their double blind study dose (50 or 100 mg/day of methadone or 80 mg TIW of LAAM) to an open dose of 60 mg/day of methadone. For the next 6 weeks the staff and patients negotiated dose adjustments as seemed appropriate, while all remained blind to the subject's previous dose and medication type. Not surprisingly, Ss who had been decreased abruptly from 100 mg of methadone or 80 mg of LAAM were quicker to ask for dose increases than were the subjects initially increased from 50 to 60 mg of methadone. However, the groups did not differ significantly in terms of the number of patients whose dose was eventually increased during the 6 weeks. The patients who started on 50 mg ended up with lower methadone doses than the other two groups, but more than two-thirds of them reached some level higher than 60 mg. The interesting finding is that

the low dose patients significantly decreased their opiate abuse during the restabilization period compared to the prior 6 weeks ($P < .05$, using an opiate abuse index similar to the one previously described). The 100 mg group increased their opiate abuse during the same period, but not significantly so. This is the first evidence in the studies discussed thus far that dose level makes a difference in opiate abuse in a group of patients who have already been stabilized on maintenance for nearly 10 months. However, these patients were on a fixed dose regimen, so the results are not necessarily relevant to patients whose dose has been adjusted in some other way during maintenance.

Berry and Kuhn (1973). This was a randomized double blind study of intermediate dose lowering during methadone maintenance. Fifty-two patients who were stable on 100 mg/day of methadone and had been in treatment an average of over 10 months were paired according to their length of time in treatment, and one member of each pair was assigned to have his or her dose reduced 10 mg every 4 weeks until the dose reached 50 mg. The remaining patients continued on 100 mg. Baseline characteristics of the two groups of subjects were similar. The duration of the study is not stated in the report, but it appears to have lasted 20 weeks -- the duration of the tapering -- but not for any further period after the full dose difference had been established. Endpoints were study retention, reasons for termination, opiate abuse, legal status, family status, employment, clinic behavior (complaints), and medical problems.

Retention to 20 weeks was 65 percent (16/26) in the tapering group and 69 percent (17/26) in the control group. The small surviving sample of 33 Ss leaves little power to detect effects on the other variables, but there were no trends favoring either group except in the number of patients living with their spouse or parental family, which increased from 74 percent to 91 percent in the tapering group and from 68 percent to 70 percent in the control group. (It was unclear whether this was a change in individual subjects or an artifact produced by attrition.) Opiate abuse data, as usual, were inadequately analyzed, but the data presented showed no trends favoring either group.

Stitzer, Bigelow, and Liebson (1979). This is a time series design, a so-called "intensive" design in which

each subject serves as his or her own control. Twenty-three maintenance clients were each given six opportunities to alter their methadone dose on a single day by as much as 20 mg, either up or down. The relevance of this study to dose effects is the investigators' attempt to detect subjective or opiate-abuse changes following these single dose changes.

No subjective effects of single-day dose increases were found. I did not find that very surprising, considering the relative insensitivity of self-report symptoms to dose effects in the studies reviewed thus far, and the fact that even opiate abuse effects of dose differences are sometimes seen only after days or weeks of a different dose level, if at all.

Goldstein, Hansteen, and Horns (1975). This study was primarily focused on the effects of allowing patients control over their own dose levels. Its relevance to dose effects is the opportunity it presented to examine opiate abuse changes that might be correlated with self-chosen dose changes.

This is a single time series design in which a policy change was instituted and subsequent events described in comparison to the same measures before the change. The new procedure was to allow clients to choose, at their absolute discretion, to raise or lower their dose by 5 mg as often as once every week, up to a maximum of 120 mg/day. If a subject's dose was above 50 mg he or she was allowed no take-home doses of methadone. Compared to a 6-week baseline period, the median dose increased only 10 mg, from 40 to 50 mg, during the 25 weeks of the study, although there was no indication that dose levels were reaching an asymptote.

The small overall increase in dose levels provides only a weak test of the relation of dose to any other variable. However, the 59 subjects were classified into four groups according to whether the general pattern of their dose decisions was to increase, decrease, vary without a predominant direction, or remain constant. Opiate abuse trends over the 6-week baseline and the first 14 weeks of the study were analyzed for each of these groups. Subjects who increased their dose (N = 18) showed a statistically significant and rather dramatic reduction in the percentage of the group showing an opiate positive test in a given week. Of the 18 Ss (31 percent) who raised their dose, about half were occasionally or steadily using

heroin during the baseline period, while by week 14 only one or two were showing opiate positives each week.

No conclusion can be reached about the pharmacological effects of the increased dose in this correlational analysis of dose and opiate abuse, since other explanations come so readily to mind. For example, subjects might choose this occasion to cut down their opiate usage because the opportunity to increase their dose or the act of asserting their control over dose enables them to avoid the anxiety that they would otherwise expect to experience. It might be informative to learn whether the dose increasers continued their low level of opiate abuse after they could no longer raise their dose, or chose not to. No other characteristics of the dose increasers were reported. Since opiate abuse tends to subside and dose levels to increase in the early months of maintenance treatment, it would be helpful to know whether dose increasers tended to be within the first few months of treatment.

Siassi, Angle, and Alston (1977a). This is a correlational study in which the relationship between dose level and abuse of other drugs was examined for patients in a maintenance clinic who had remained in treatment for at least 2 years. Of 266 patients in treatment at some time during a 2-year period, 57 (21 percent) met the length-of-stay criterion. Mean dose levels were calculated and two contrast groups formed, one group of 27 with means below 60 mg (mean 48 mg) and one group of 19 with means above 80 (mean 86 mg), discarding the middle dose level group and leaving 46 subjects. The two groups did not differ significantly from each other or the general clinic population on age, years of addiction, arrests, sex, education, race, marital status, or employment. The two dose groups did not differ from each other in their use of opiates or amphetamines. The low dose group tended to use more sedating drugs, in that more of them showed urine tests positive for barbiturates and for ataractics, and to describe themselves more frequently as alcoholic on the Michigan Alcoholism Screening Test. This greater usage of sedating drugs by low dose patients has not been reported in the fixed-dose prospective studies already reviewed, so it is unclear whether the association only appears in flexible-dose environments, or there was some unusual circumstance in this site that led to this association. Until it is confirmed elsewhere it is hard to know what to make of it.

Havassy, Hargreaves, and De Barros (1979). This was a randomized open trial of self-regulation of dose. In two clinics, 116 maintenance patients who agreed to participate were randomly assigned to one of three conditions: simple self-regulation, self-regulation with an incentive (increased take-home privileges) for dose reduction, and standard treatment. Endpoints were dose level and opiate abuse. In one clinic, a subgroup of those on simple self-regulation (those starting at prestudy dose levels of 46-65 mg) increased their dose significantly (an average increase of about 20 mg in 6 weeks), then returned, on the average, to their prestudy level by week 16. The simple self-regulation group (in this same clinic) transiently showed significantly lower opiate abuse than the other groups, but not only among the specific subjects who raised their dose.

The study was continued to 48 weeks in the clinic where this first effect was seen, and all groups remained on similar dose levels and showed similar rates of opiate abuse (Havassy and Hargreaves 1981). Thus the correlation of dose increase and opiate abuse reduction seen in the Goldstein et al. (1975) self-regulation study was not nearly as evident in this study. The fact that a subgroup of patients in the simple self-regulation condition transiently raised their dose lends itself to several interpretations. It could be that these patients expected a dose increase to be beneficial, but over the next 4 months changed their mind about its value. It could also be that they were seeking a short-range benefit from an increased dose, and may have experienced that benefit, then returned to a lower maintenance dose for the long run. It seems to me that neither interpretation can be made with much confidence.

Goldstein (1970; 1971; 1972b; 1972c). In these papers Goldstein alludes to a single blind study comparing 30, 50, and 100 mg stabilization doses in addicts newly admitted to maintenance. Subjects were started on 30 mg and increased 10 mg every day until they reached their assigned stabilization dose. The increase interval was later lengthened to every 2 days; it is unclear whether that applies to any of these subjects or not. This was one of the earliest well designed dose comparison studies, but the results have never been reported in reviewable form. A total sample of 206 subjects is mentioned in one paper. Some subset of these were included in the randomized trial. Endpoints were said to be a 30-item symptom self-report at baseline, 2 weeks, and 1, 2, 3, 6, 12, and

24 months, and random urine tests one day in five, but no analyses of these endpoints were presented. Of the subset of subjects who were randomized to dose, no information is reported on the success of the randomization in equalizing subject characteristics at baseline, or whether differential attrition occurred. The degree to which subjects were kept on their assigned dose is not reported, although the investigator states that while he intended to follow all subjects for 3 months on a fixed dose, some exceptions were allowed.

Goldstein (1970) describes the results of patient's first 3 months on the program for 20 subjects on 30 mg, 80 subjects on 50 mg, and 106 subjects on 100 mg. Elsewhere he implies that these 206 subjects included some who were not randomly assigned. Nevertheless, he summarizes results on these 206 subjects as follows: "As measured by urine test results or by questionnaire data, we find a more rapid suppression of heroin use with 100 mg than with lower doses, but the results in all three groups tend to converge after the first month. There was little difference between the doses by the third month, although what marginal differences there were favored the 100 mg group. There was also no evident influence of dose upon absenteeism, dropout rate, or the number of arrests." It is tantalizing to hear of these interesting results, yet not have them presented so that they could be evaluated. In a later paper Goldstein (1971) alludes to a comparison of 30, 50, 80, and 100 mg. I assume these doses were not all used in the same study, but that he is referring to the set of studies reviewed above. He also mentions "special studies" of doses up to 200 mg, which also have not been reported. A few more details were given in a paper at the Fourth National Conference on Methadone Treatment (Goldstein 1972c), where this study is described as lasting 35 weeks, in which "a number of patients" were given blind dose increases from the 50-100 mg level to doses as high as 250 mg, then reduced again to 80 mg. He reports that "provided the rate of change was slow . . . no improvement was seen with increasing dose," where improvement refers to symptom complaints and opiate abuse. Thus there seems to have been some suggestion that rapid increases at least briefly suppress not only symptom complaints but also opiate abuse.

Stitzer, Bigelow, and Liebson (1981). In this study a 20 mg dose increase was given abruptly under single blind conditions to each of eight subjects. Endpoints were the total score on a 56-item symptom rating scale completed

twice weekly for 3 weeks before and 3 weeks after the dose change, plus opiate abuse from urine tests performed twice weekly on a fixed schedule. As a group there was a statistically detectable reduction in symptom scores after the dose increase. Plots of individual subjects showed that six of the eight subjects accounted for the effect. Individual symptom curves were quite variable and this reviewer found the changes not very convincing. They tended to be most evident for about a week following the dose increase, after which three of the six that showed a reduction returned toward their baseline high level of complaint. Of the four subjects who showed opiate positives during baseline, with values of 17 percent, 50 percent, 67 percent, and 83 percent of urines positive for opiates, the first three showed no opiate positives after the increase. While there were only four subjects for whom opiate abuse was relevant and only a very brief follow-up period, this latter outcome might be worth further study focused directly on patients with persistent opiate abuse.

Jaffe (1970b). This was a single blind randomized trial comparing a doctor's choice dose regimen to a similar regimen with arbitrarily imposed 10 mg increases during 6 or 7 of the first 27 weeks. The randomization was poorly done, resulting in an initial imbalance in the size of the groups, 76 in the doctor's choice regimen and 50 in the higher dose regimen, thereby reducing statistical power. However, the demographic characteristics of the two groups were reasonably balanced at assignment. Attrition was 42 percent by 36 weeks and was imbalanced, the low dose survivors having a higher proportion of initial employment. The intended dose differentiation was not implemented, the high dose group not reaching a stable average of 90 mg until the final 10 weeks of the study. The average dose in the doctor's choice (low dose) group rose steadily from 36 mg at admission to 53 mg at 36 weeks, but it is unclear what portion of this change is due to dose increases and what portion to the selective dropout of patients on lower doses. The variability of dose within each group was high, the reported standard deviation being larger in the low dose group, suggesting that selected low dose patients judged to need a higher dose were treated at 80-100 mg. The meaning of this dose comparison therefore seems totally obscured.

Endpoints were retention, opiate abuse, and employment. Retention was equal in the two groups. Opiate abuse figures varied widely depending upon how one counted missed

samples, but the investigators had no records to enable them to distinguish refused samples and missed clinic visits from excused samples due to staff error or to take-home privileges. Therefore the opiate abuse data are probably uninterpretable. The employment outcomes, which were the same in both groups of survivors, are uninterpretable because of the biased attrition from the two dose groups.

Berry (1972). This was a comparison of 30, 50, and 100 mg fixed dose regimens in which patients were systematically and nonrandomly assigned at admission. Two hundred patients were thus assigned and outcomes are reported after 4 months of treatment. The numbers assigned to each group are not reported. It was reported that drug history, criminal history, current legal status, job status, and "many more subjective evaluations of his psycho-social situation" were taken into account in selecting a dose level, but nothing was said about how these characteristics were taken into account. Endpoints were retention, opiate abuse, arrests, employment, and family role functioning. None of these variables showed significant differences at 4 months, although there was a higher incidence of amphetamine use in the 100 mg group. No statistical tests were described. However, reported precentages of retention and opiate positives were quite similar across groups. Total retention was very poor at 4 months, reaching levels usually seen at 12 months. Low, middle, and high dose groups retained only 56 percent, 54 percent, and 60 percent, respectively. Among the approximately 110 subjects remaining, opiate abuse was low (12, 17, and 12 percent), suggesting that the program tended to eject nonconforming or nonimproving patients.

The author concludes that either dose does not make any difference, or all the patients who needed to be were correctly put onto a higher dose (with perhaps some others who would do equally well at any dose). A third possibility is that their unusually high early attrition extruded the subjects for whom dose makes a difference. These various possibilities make it impossible to draw any firm conclusions from this study.

Handal and Lander (1976). This correlational study of 155 maintenance patients found that high dose was associated with fewer missed visits and lower opiate abuse, but only early in the history of their program. Later, when most patients had been on maintenance for over 4 months, the association disappeared. The observed association seems

most likely to be an artifact of the increasing average dose and concurrently decreasing average abuse rate, both a function of time in treatment up to 6 or 8 months after induction. This will spuriously produce a correlation between dose and opiate abuse when most patients are in this early phase of maintenance.

Perkins and Bloch (1970). In a retrospective correlational study of 521 patients, a significant positive correlation was found between methadone dose (above 80 mg or not) and the patient being still retained in treatment. As with the previous study, a spurious correlation would be expected due to two factors: one is the general rise in average dose as a function of time from admission, which would lead to higher average dose in retained patients, who have typically been on the program for a longer time; the second factor is the suppressing effect on a patient's mean dose level of a long period of tapering off the program, which will more frequently be seen among discharged patients than retained patients.

Brown, DuPont, Bass, Glendinning, Kozel, and Meyers (1972). This is a correlational study of the relationship of doctor's choice dose to outcome. Two hundred seventy-three subjects were dichotomized into those receiving 60 mg or more at their last recorded visit (N = 207) compared to those who received less than 60 mg (N = 66). Those being detoxified at their most recent visit were excluded. Endpoints were retention in treatment (15 months after the program opened but varying times after patient induction), opiate abuse, arrests, and employment. High dose patients showed 61 percent retention compared to 23 percent on low dose ($P < .01$), leaving 15 survivors in low dose for the remaining comparisons, which are therefore not very meaningful. The correlation of dose with retention is probably spurious, the direction of causality going the other way. Subjects terminating early in treatment will have been less likely to have reached a high dose than those remaining in treatment, since group average doses typically rise as a function of time from admission under conditions of heterogeneous doctor's choice dosing.

Bowling, Moffett, and Taylor (1973). This is an early correlational study of 131 patients, currently in treatment, 57 of whom were receiving 140 mg or more, and 74 who were receiving 70 to 80 mg ("low dose"). Endpoints were opiate abuse, nonopiate drug use, employment, and arrests, none of which differentiated the dose groups. The mean

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time in treatment for the high dose group was 22.6 months compared to 12.9 months for the low dose group, illustrating the general tendency for dose level to be positively correlated with time in treatment among retained patients. The failure to find differences means either that there is no dose level effect, or that they chose doses wisely, or that patients who did not do well on the dose they received tended to have already terminated treatment. Therefore the results cannot provide evidence for the lack of a dose effect.

McGlothlin and Anglin (1981b). This is a very impressive 6- to 7-year follow-up of 1971-1973 admissions to three maintenance programs, two of which pursued a high dose, long-retention policy, while the third used low doses and a relatively strict policy with respect to involuntary termination for program violations. Outcomes were poorer in the latter program, but the confounding of dose policy with retention, and probably other differences in the style of staff-patient interaction preclude any conclusions about dose as such, even though the findings would be consistent with a superior effectiveness of higher doses.

Langley, Norris, and Parker (1973). This is a correlational study of 144 patients, examining dose level, opiate abuse, and length of time in treatment, along with additional interview-based information. An attempt was made to relate dose level to opiate abuse in subgroups of patients having different lengths of time in the program. No statistical tests are reported, the subgroup sample sizes are very small, and all is presented in such an unfocused fashion that I could not determine what relationships they had found.

Siassi, Angle, and Alston (1977b). This is a correlational study of patients discharged from a program during a 2-year period. Of 114 patients who had been in treatment at least 21 days and had been discharged and not readmitted within the 2-year period, high and low mean dose groups were selected. Twenty-eight patients between 60 and 80 mg were excluded, leaving 33 low dose patients (mean 48 mg) and 53 high dose patients (mean 86 mg). Patients were further classified as treatment successes or failures. If for 3 months they had functioned in a work/educational/homemaking role, and were thought to have abstained from illicit drugs and criminal activity, and subsequently completed detoxification by mutual consent, they were considered treatment successes. Seventy-two

percent of the high dose patients were considered treatment successes but only 30 percent of the low dose group ($P < .001$). As with other correlational studies of this type, high dose was associated with longer program retention (748 days vs 393 days), and this could spuriously account for the association of dose level with outcome via the association between program tenure and dose.

Craig (1980). This is a single-group descriptive study that purports to show that "methadone maintenance averaging 30 mg/day achieved similar 'success' rates as other studies using larger daily doses, but did so at the expense of retaining fewer clients in treatment." To call a 10 percent 12-month retention rate "retaining fewer clients" seems a bit understated. What they showed was that they lost from the program a group of clients of significantly poorer prognosis, but that by extruding more poor-prognosis patients they could show that the 10 percent they retained were doing reasonably well. A 12-month follow-up of early (30-day) dropouts showed that they had made little progress, while retained patients were doing much better. The author argues that this is evidence for treatment effectiveness, but of course the treatment effect is confounded with differential prognosis, the improvement of the retained patients presumably resulting from both factors, but in unknown proportion.

Conclusion: There Is a Dosage Effect Early in Maintenance

The Ling et al. (1976) VA collaborative study seems to me to provide, by itself, persuasive evidence that a 100 mg fixed dose is more effective than 50 mg in suppressing opiate abuse during the first 5 to 10 months of maintenance. I argued that the lower bound on the size of the effect as estimated from that study was large enough to be of clinical importance. The finding certainly does not suggest that all patients should be maintained on 100 mg. The finding does imply that at least 10 percent of patients, and probably more, will do better if maintained on some dose higher than 50 mg during their first 5 to 10 months in treatment.

I then examined the other five studies from which I think one can draw causal inferences. Goldstein and Judson (1973), Jaffe (1970a), Ling et al. (1980), and Berry and Kuhn (1973) all seemed not to contain any evidence that contradicted the finding from Ling et al. (1976). Garbutt and Goldstein (1972) are not consistent with it, but this

is an isolated finding (lower retention on 100 mg in the first 13 weeks) in a study with many limitations, and I have argued that in the absence of a convincing reconciling explanation, the Garbutt and Goldstein finding should not override the stronger Ling et al. (1976) findings.

Considering still the 5 to 10 months of maintenance, we have less information about other dose comparisons. The only randomized trial that is relevant to dose levels over 100 mg is the Goldstein and Judson (1973) comparison of 40, 80, and 160 mg. The problems in this study make it almost useless for ruling out a difference in effect between 80 and 160 mg. One would expect such a high dose, if it is to be useful at all, to be differentially helpful in suppressing opiate abuse in patients for whom this is a persistent problem. Goldstein (1972c) and Stitzer et al. (1981) also hint (very speculatively) that abrupt increases may be more effective than gradual increases in suppressing opiate abuse, at least temporarily. But the Goldstein and Judson (1973) study examined 160 mg in a patient group showing very little opiate abuse at baseline, and raised doses at the rate of only 10 mg per week. Thus the study may have been essentially irrelevant to the most plausible uses of dose levels over 100 mg. With its brief exposure time of 18 weeks and absence of power to test effects on opiate abuse, it can certainly not be said to have ruled out the superiority of very high doses among opiate abusing patients. Goldstein and Judson (1974) allude to other studies of high doses, but they have not been published. However, even were it found to be true that abrupt dose increases interrupt a pattern of persistent opiate abuse, it would need to be demonstrated that this affects the long-term course of such maintenance patients. Goldstein (1972c) seemed to reach the conclusion that it would not.

Current policy attention is not primarily focused on doses over 100 mg but on the lower end of the scale. The widespread use of 20 to 40 mg, and the pressure in some states to restrict doses to these low levels is more central at the moment. There are two issues: should we make it very difficult to use dose levels of 80 or 100 mg; and are the currently typical dose levels of 20-39 mg (NIDA Services Research Branch 1979) high enough to be effective with as many patients as now receive them?

If 100 mg is a more effective dose than 50 mg for at least some patients (during the first 5 to 10 months of maintenance), and more effective to a clinically important degree as I have argued, then it seems a compelling corollary that 100 mg is also more effective than 40, 30, or 20 mg for some patients. For smaller differences in dose one would not expect to see differences in effect that are as large (or that are seen in as large a proportion of patients), although we need not assume that equal ratios or increments of dose will correspond to equal ratios of effect. The rather abrupt increase in symptoms frequently experienced by patients detoxifying from maintenance when they reach about 20 mg should keep us alert for threshold phenomena.

There have been three attempts to compare 30 to 50 mg dose levels. The Garbutt and Goldstein (1972) study is the strongest of these, but in my view it failed to find any clear evidence that 30 mg is inferior to 50 mg. The second study of 30 vs 50 mg (Goldstein 1970; 1971; 1972b) has never been adequately reported. The Berry (1972) study, while it compared 30, 50, and 100 mg fixed dose regimens, assigned patients to these regimens on the basis of clinical judgment, so the similarity in outcomes is not evidence for the adequacy of 30 mg for all patients. A fourth descriptive report by Craig (1980) of a single group of patients maintained on doses in the 30 mg range reported a strikingly low 10 percent 12-month retention rate, but in the absence of a higher-dose comparison group in the same clinic, it is entirely possible that the low retention rate had nothing to do with dose. In summary, we have virtually no evidence that a 30 mg maintenance regimen is inappropriate to use for a large group of patients, so long as all patients are not rigidly restricted to this dose level. This contrasts with the opinion among many clinical leaders that 30 mg is not adequate during early maintenance. In view of the widespread use of this dose, I suggest that this is an important issue for further research.

This controversy could probably be resolved if we understood more about individual differences in dose requirements. There have been a few case reports of idiosyncratic metabolizers (e.g., Walton et al. 1978). Kreek, in her review of factors modifying the pharmacological effectiveness of methadone (this volume, part I, chapter 3), notes concurrent medication or medical conditions that can modify the disposition of methadone in the body. But

these factors probably do not account for all of the individual variation in dose requirements. Not only do we lack evidence about who needs the higher doses--there is even little description of the patient characteristics that lead clinicians to assign higher doses to some patients. One hears and reads allusions to using a low dose when the patient expresses a preference for this, and using higher doses with patients showing more severe psychopathology, more persistent opiate abuse, or more persistent complaints that methadone is "not holding." Treece and Nicholson (1980) made careful DSM-III diagnoses of 31 maintenance patients and found evidence for differential dosing of three diagnostic subgroups. They found a subgroup of schizoid, schizotypal, and paranoid personalities (N = 5) who showed a mean dose of 87 mg. By contrast, 19 subjects with histrionic, narcissistic, antisocial, and borderline personality disorders had a mean dose of only 48 mg, and 7 subjects with avoidant, dependent, compulsive, and passive-aggressive personality disorders showed the lowest mean dose, 36 mg ($P < .001$). Such correlation of patient characteristics with dose is evidence that clinicans have hypotheses about who needs higher dose levels. It is time, I think, to determine whether some of these hypotheses have validity. Is it a particular diagnostic subgroup that needs higher doses, or those with persistent opiate abuse, or complainers, or only atypical metabolizers? If some or all of these groups need higher doses, how important is dose adjustment for their outcomes? The fact that a small general dose effect seems to be present in unselected patients suggests that there is some subgroup for whom the correct dose makes a large difference in outcome, at least during the crucial early months of maintenance when patient attrition is highest.

Dose effects after the first year of maintenance have been little studied. It is clear from several of the descriptive papers that dose tends to increase as a function of time in treatment, at least in programs that do not have an ideology focused on limiting dose levels. However, there have been no prospective studies comparing, say, 30 mg vs 60 mg among patients in treatment at least a year who are not showing continuous opiate abuse.

So what is an appropriate regulatory stance about dosage? Since there is persuasive evidence that 100 mg is superior to 50 mg during the first 5 to 10 months of maintenance for an important subgroup (10 to 30 percent) of patients,

regulations that discourage individualized dosing are inappropriate. Any regulation that requires special permission to exceed some dosage level effectively eliminates the use of higher levels except for a tiny fraction of patients where the physician has specific evidence of need, and even here the cost in clinician effort to get the permission will be prohibitive in its effect, especially as funding levels per slot are reduced by inflation. Therefore NIDA should encourage state agencies to adopt regulations that freely allow the use of dose levels up to at least 100 mg.

TREATMENT DURATION AND EFFECTIVENESS

The issue of treatment duration is, by its nature, much more difficult to examine scientifically than the issue of dose. We can see some dose effects in 1 day, other dose effects in a few months. But the durations at issue are not a matter of 1 month versus 9 months. It is so well accepted that 3-week maintenance (sometimes called outpatient detoxification) is less effective than 3-year maintenance that it did not seem important to review the evidence. The policy issue is whether maintenance should be operated so that 50 percent of the patients have terminated within 12 months (most commonly reported figure), or whether we should strive to keep almost all patients in treatment indefinitely. No one has attempted a controlled trial comparing different durations of maintenance. Consider a controlled comparison of 1-year to 3-year maintenance--it would require a decade and a million dollars to carry out such a study, even after we had solved the feasibility and ethics problems. Therefore we must examine here a few correlational studies that pick away at the edge of the question. Table 5 lists the design relevance of the seven studies that seem to bear on the effectiveness of treatments of different duration. In table 5 I have used many of the same characteristics that were used to evaluate the dose studies, except that the nature of the "blind" is irrelevant, and follow-up time is substituted for time of exposure to the treatment comparison.

Review of Studies

McGlothlin and Anglin (1981b). This was a 6- to 7-year follow-up of 347 1971-73 male first admission patients in three maintenance programs, two of which (A and B) pursued

Table 5. Design relevance of studies of the effect of maintenance treatment duration on outcome

Review	Reference						
Criteron	McGlothlin, Anglin 1981b	Stimmel et al. 1978	Dole, Joseph 1978	Dole, Joseph 1977	Cushman 1978a; 1978b	McGlothlin, Anglin 1981a	Simpson 1981
Comparison	3 programs	stay length type of discharge	retained vs discharge	retained vs discharge	none	program closed	stay length
Endpoints	Comprehensive	opiate abuse	opiate abuse arrests alcoholism	opiate abuse arrests alcoholism	opiate abuse overall index	comprehensive	overall index
Design	Intact groups	correlation	correlation	correlation	descriptive	intact groups	correlation
Sample size	347	429	1413	347	513 (89)	177	389
Follow time							
In methadone maintenance			72 months	not reported	not reported	30 months	16+ months
Post methadone maintenane		60 months		not reported	35 months	26 months	12 months
Total	84 months		120 months			56 months	
Group match	fair	na	not reported	not reported	na	good	not reported
Attrition	9%	low	8%	63%	28%	5%	not reported
Biased loss	na	na	na	not reported	not reported	na	not reported
Confounding	probable	probable	probable	probable	na	probable	probable
Statistics	excellent	excellent	weak	weak	adequate	excellent	adequate
Inference	correlational	correlational	correlational	correlational	suggestive	suggestive	suggestive

a high dose, long-retention, flexible conformance-to-rules policy, while the third (C) used low doses and a stricter policy of involuntary termination for program violations.

The programs were quite distinctive in their policies. Mean stabilization doses for programs A, B, and C were 95, 82, and 43 mg. The percentages of subjects initially stabilized at less than 40 mg for A, B, and C were 0, 1, and 31 percent; the percentages at 60 mg or more were 96, 89, and 9 percent. From 1972 to 1978 the three dose policies remained distinct although the subjects still in treatment had somewhat lower doses in A and B than those on which they were initially stabilized. Mean time to first discharge in A, B, and C was 44, 25, and 14 months. The percentages still active in treatment at follow-up interview were 24, 8, and 1 percent, and the percentages detoxified under program supervision were 12, 18, and 2 percent. By contrast, the percentages who just "stopped coming" were 10, 16, and 29 percent, and the percentages discharged for program violations were 18, 22, and 44 percent. The mean percentages of nonincarcerated time spent receiving maintenance treatment from original entry to follow-up interview were 70, 59, and 43 percent. Thus it can be seen that A, B, and C formed a continuum in dosage and duration practices, although B was much closer to A than to C.

The original sample was 347: 138 in A, 99 in B, and 110 in C. Only 4 percent were not located 6-7 years after admission, 5 percent refused, and 5 percent were dead, for an impressively low 14 percent attrition rate, leaving a usable sample of 297. Not surprisingly, study attrition was the highest (21 percent) in program C. Whether there was differential attrition of subjects with different baseline characteristics was not reported. There was reasonable comparability of subject characteristics across programs, although C had fewer minority patients, and A had an older, longer-addicted group. In their statistical analyses the authors provide convincing evidence that this baseline imbalance does not account for the findings.

Endpoints were the most comprehensive and coherently organized of any I have seen in the follow-up study literature. They were assembled into ten measures, six of which significantly differentiated the three programs, all but one showing program C to have the poorest outcome. Three of the four nonsignificant measures showed similar

trends. Endpoints, generally shown as mean percentage of nonincarcerated time, are given in table 6.

An interesting feature of this study is its analysis of "social cost." Arrest, trial, incarceration, legal supervision, property crime losses, and welfare costs per year were calculated for the years from first daily narcotic use to program admission; then these same costs plus treatment costs were calculated per year for the years from treatment to follow-up. The estimated annual costs of subjects in programs A, B, and C, as a percentage of pretreatment costs, were 47, 62, and 85 percent. It would appear from this that program A, the most expensive because of its long retention time, is also the most cost effective, netting a 53 percent saving in social cost compared to only a 15 percent saving for program C.

This is a unique and thought-provoking analysis that bears directly on important policy questions. However, the analysis deals only with the costs associated with the patients who were treated. With mean percentage time on maintenance from admission to follow-up (80 months later) of 70, 59, and 43 percent in programs A, B, and C, respectively, program C should be able to treat more patients per slot than the other programs. These differences are taken into account in table 7, which shows an extension of the McGlothlin and Anglin social cost estimates to derive benefit/cost ratios for the three programs. The high dose, long-duration programs still show superior benefit/cost ratios, but the differences are not so large.

The major problem in considering the policy implications of this study is its confounding of dose policy with the policies about duration and confrontation regarding rule conformity. In this respect these programs are representative of a very prominent stylistic dimension that differentiates the majority of programs in the country, judging by a recent survey by Brown and others (Brown, personal communication, 1981).

There is a methodological aspect of this study that I think is an important contribution to the way we look at maintenance outcomes. It reminds us that outcome is a system of interrelated performances, not simply abstinence from heroin. McGlothlin and Anglin have demonstrated that one can develop plausible information about these variables using a single retrospective interview as the major data source, but recording estimates of the important subject performances for each of the time periods of interest

Table 6. Outcomes in three programs with contrasting dosage and duration policies

Program characteristic	Program A	B	C	P
Arrests/man-year	.78	.96	1.72	NA
Mean percent time incarcerated	13	17	22	.001
Using opiates daily	14	19	37	.001
Using no opiates	54	39	34	.001
On legal supervision	54	51	49	NS
Abusing alcohol	38	42	35	.025
Dealing	18	25	39	.004
Employed	58	62	52	NS
Crime days/year	24	36	70	.001
Property crime income ($)	3400	3400	7600	NS

Table 7. Benefit/cost estimates for three programs differing in dosage and duration policies

Program charcteristic	Program A	Program B	Program C
Annual social cost before treatment	$19,300	$16,900	$19,100
Annual social cost after treatment	9,100	10,500	16,300
Savings/year	10,200	6,400	2,800
Slot fraction	.70	.59	.43
Savings/slot/year	14,517	10,847	6,512
Slot cost	2,400	2,400	2,400
Benefit/cost ratio	6.1	4.5	2.7

(McGlothlin et al. 1977). By not focusing exclusively on abstinence they keep in view the degrees of personal and public change that may result from treatment interventions even when abstinence is achieved only sporadically or not at all.

Finally, this study gives us the kinds of statistics with which we are all too familiar: an average of 6.8 years after admission, only 18.5 percent of the subjects are not on maintenance and not readdicted. Compared to those re-addicted or readmitted, these "successes" were initially on maintenance 32 months compared to 18 months ($P < .05$), and during their initial maintenance they were more likely to be free of opiate abuse (65 percent vs 40 percent, P .05) and employed (70 percent vs 48 percent, $P < .05$).

Stimmel, Goldberg, Cohen, and Rotkopf (1978). This was a follow-up study of 429 patients detoxified from a maintenance program serving East Harlem. Eighty-eight (21 percent) were judged by staff to have completed treatment satisfactorily, while the remainder were detoxified under other circumstances. Treatment completers were treated an average of 40.9 months while all others were treated an average of 14.2 months ($P < .005$), and completers remained narcotic free an average of 6 months longer than non-completers. A positive association was also found between duration of treatment and percentage remaining drug free, regardless of the reason for discharge. These percentages were 14 percent (1-11 months), 21 percent (12-23 months), 33 percent (24-35 months), and 40 percent (more than 35 months). In a sophisticated Cox-model analysis of relative contribution to risk, treatment completed vs other detoxification, when entered first into the analysis, showed a 4.7 relative risk, while months in the program added a highly significant but small additional increment in prediction. Since these two factors are so highly correlated, the reverse would be true if length in treatment were entered first. It would have been informative to know the relative risk associated with length of treatment as the variable entered first. The authors imply but do not state that it would make a smaller contribution than type of discharge. Curves for the cumulative probability of remaining drug free are given for treatment completers and other detoxifiers, for 48 months after termination (60 months for the "other" group).

This is a very useful and competently presented follow-up analysis of treatment outcome. It is limited, of course, by its unknown generality beyond large inner-city programs

serving ethnic minorities and using relatively high dose levels.

Preliminary reports of this study also appeared in Stimmel and Rabin (1974) and Stimmel et al. (1977).

Dole and Joseph (1978). Two cohorts of maintenance patients were followed from admission, one cohort for 10 years, another for 5. The first cohort was all persons (64 percent) admitted to maintenance treatment in New York City in calendar years 1966-67, and the second was a stratified random sample of 897 from the 17,000 persons first admitted in 1972. Subjects were interviewed and supplementary records were examined. Data were obtained on 1,413 (92 percent) of these two groups. Retention in treatment of the first cohort was high, 75 percent still being in treatment after 5 years. In the 1972 cohort only 41 percent remained in treatment after 5 years, which is still considerably higher than reported by others for mid-1970s admission cohorts. Dole and Joseph report that opiate abuse is vigorously suppressed during treatment, even for those subsequently discharged (about 10 percent of 846 patients), but rebounds to about 70 percent soon after discharge. Of the 846 discharged, 167 (20 percent) were deemed to have "completed treatment," and of these, 34 percent were doing well after discharge, compared to only 1-2 percent among dropouts and administrative discharges. The findings support the authors' argument that few patients can be expected to leave maintenance and remain abstinent, and funding and regulatory policies that encourage brief treatment reduce the degree to which addicts who enter maintenance will be rehabilitated. Unfortunately the follow-up data are not organized to estimate risk factors and relapse functions (cf. Stimmel et al. 1978) that might be more helpful in estimating the effects of various policy options.

Dole and Joseph (1977). A random sample was drawn of 461 patients out of 5,571 who entered maintenance during 1972 in New York City and who were not in maintenance treatment in 1974. For comparison, an equal sample was drawn from the 11,994 who entered during the same year but remained in treatment. Outcome information was obtained for 202 (44 percent) of the discharge group and 143 (31 percent) of the group still in treatment. Only 11 percent of the discharged group was not abusing opiates, alcohol, or other drugs, while this was true for 53 percent of those in treatment. More than weekly opiate abuse was seen in 59 percent of the discharged group and only 1 percent of

the group still in treatment. Two qualifiers of these findings are that the authors did not distinguish different types of discharge, nor examine the relative prognosis at admission of those discharged compared to those still in treatment. Thus the findings do not provide a measure of treatment effectiveness, but they do put a limit on the expected outcome of discharged patients.

The authors deplore the fact that by 1976 the 12-month retention rate in maintenance treatment had fallen to about 60 percent, and lower in other parts of the country, since these follow-up results indicate how few discharged patients remain abstinent.

Cushman (1978a, 1978b). One hundred sixty-one (72 percent) of 225 patients who completed detoxification from a maintenance program were followed up to 8 years. Of these, 23 percent were stable and narcotic free 2.9 years after detoxification. Of 89 "therapeutic detoxification" patients, this figure was 42 percent. Relapse rate among these patients declined as a function of duration of post-maintenance abstinence, being 19 percent, 10 percent, 4 percent, and 0 percent among those at risk in the first, second, third, and later years. The frequency of enduring abstinence was 9.7 percent among the total treatment sample of 522 over an 11-year period, so that about 1 percent of these maintenance patients achieved abstinence each year. Among these 89, relapse was related only to being unemployed at the completion of detoxification ($P < .01$), and not to duration of treatment (mean = 4.06 years), alcoholism, marital status, or sex.

McGlothlin and Anglin (1981a). Using methods similar to their larger 7-year follow-up of three California maintenance programs (McGlothlin and Anglin 1981b), the investigation capitalized on a natural experiment, the closing of the only methadone program in the relatively isolated rural community of Bakersfield, California. A 2-year follow-up was conducted of the 99 patients enrolled when the closure was announced. Because of the remote location, only 11 transferred to another clinic. A sample of 88 was selected from a continuing program in a similar rural community for comparison. All were interviewed approximately 26 months after discharge (or after a matched dummy discharge date in the comparison group), using a method for collecting retrospective longitudinal data (McGlothlin et al. 1977). Endpoints included arrests, incarceration time, legal supervision, opiate abuse, alcohol abuse, drug dealing, property crime, employment,

welfare, treatment, family situation, dependent support, time in current residence, health, and monetized versions of some of the endpoints combined into "social cost."

The results were mixed. While there were consistent trends for the sample from the closed program to do worse on several measures (enough worse to be of clinical importance, in my opinion), sample sizes were too small for these observations to be statistically reliable. Men and women showed somewhat different patterns of effects, reducing effective sample sizes even further. The mean annual social cost among the men from the closed program in the 2 years after discharge was $6,204, only modestly higher than the $5,323 of the comparison males. For the women, the discharged group actually showed a lower social cost than the comparison group ($3,691 vs $6,306). While it seems clear that there was considerable personal cost to many patients when the program closed (possibly including two drug-related deaths), the only statistically reliable difference from the comparison group was an increase in arrests. The authors caution against overinterpreting this finding, since it seems to have been largely accounted for by a specifc and temporary increase in surveillance of addicts and arrests on misdemeanor "under-the-influence" charges, which carried a mandatory 90-day jail sentence. This factor plus a very low quality and high price for street heroin may have limited the readdiction rate in the discharged group, the authors suggest.

At the time of the follow-up interview, 73 percent of the discharged sample were not incarcerated, were not on methadone, and did not admit opiate abuse, compared to 28 percent in the comparison group. This percentage drops to 49 percent when urine tests and refusals are taken into account, vs 19 percent in the comparison group. These outcomes are certainly more favorable (for the patients, not for the programs) than one would have predicted from the New York City studies reviewed above. While East Harlem may not be quite the same as Bakersfield, California, the authors raise the issue of the trade-off between the unnecessary prolongation of addiction by methadone maintenance, as against the severe disruption of stable social functioning seen in some of the discharged patients. The authors point out that a policy of enforced termination of maintenance after a fixed time is being adopted by some programs, and suggest that the risks of such a policy may be partially reduced by adopting a flexible readmission policy.

Simpson (1981). This is one of the papers derived from the Drug Abuse Reporting Program (DARP) follow-up study. It relates length of time spent in the index DARP treatment to outcomes 1 year after the end of that treatment. Only the 389 subjects originally in maintenance are relevant. The endpoint was a composite outcomes score that could range from 5 to 15 and included items in five areas: criminality, opioid use, nonopioid use, alcohol use, and productive activities. Treatment tenure was analyzed in four categories that produced approximately equal subsamples: 1-90 days, 91-240 days, 241-480 days, and more than 480 days.

Mean composite scores for these four tenure groups were 10.58, 10.71, 11.05, and 11.76 ($P < .01$), showing that those in treatment longer had slightly better outcomes 1 year after the end of their index treatment. In another analysis using equal-sized time intervals, it was found that this relationship corresponded to a correlation of 0.20 and that the relationship of tenure to composite outcome was linear (correlation ratio = .22). This focused analysis of maintenance outcomes confirmed in more detail the same finding reported previously from these data by Simpson et al. (1979), and from an independent sample by Simpson (1979).

I found it hard to interpret this correlational result. Presumably persons with different length of stay differ in baseline prognosis, as has been found by others. Simpson argues that since those treated less than 90 days in maintenance have outcomes similar to intake-only or outpatient detoxification patients, there is "no evidence that the DARP groups were systematically biased with respect to patient assignments." Unfortunately, it is also not evidence that they were equal, but only that early dropouts from maintenance may be similar to the comparison groups.

It has also been clear from the other studies reviewed here that within-treatment opiate abuse, employment, and arrests tend to show better results as time from admission increases. This effect partly reflects individual improvement over time, and partly the selective termination of patients with a poorer prognosis. Furthermore, follow-up studies often show some degree of improvement in minimally treated or untreated groups as a function of the passage of time. Since the outcomes in this study were assessed one year after treatment termination, the length

of time between baseline and follow-up assessment is completely confounded with the length of treatment, and could spuriously produce the small observed correlation.

It is correct that these correlational results are consistent with the presence of a treatment effect, and a greater effect the longer the treatment. As a clinician, my experience also tells me this is true. Nevertheless, with the number of plausible alternative explanations and the very small size of the relationship (4 percent of outcome variance is associated with program tenure), I think the author overstates his results when he says his findings "support the effectiveness of drug-abuse treatment." I do not think these results bear on the policy issues regarding the duration of maintenance treatment.

Conclusions Regarding Maintenance Duration

The most prominent phenomenon in the clinical lore affecting duration is dramatized by the recent Brown et al. survey of program practices (Brown, personal communication, 1981). This is the association of high dose with long duration of treatment. High dose and long duration are traditionally also associated with a flexible and supportive rather than confrontational treatment philosophy. It is psychologically and ideologically understandable that program policies toward dosage, duration, and rule conformance should have come to be associated. But is there any logical or empirical basis for expecting these three policies to have the same causal relationship to outcome? I think not, and I think it is time to examine the separate effects of these three components of treatment philosophy.

One consistent finding is that in New York City it is very hard to complete maintenance treatment and remain abstinent. Even the 2 percent cream of the crop who can voluntarily detoxify in a good year have only a one-third chance to remain abstinent, although the specific figures probably vary from program to program. This has led several of these investigators to argue for a policy of indefinite maintenance duration for the majority of addicts. Other writers such as Goldstein (1972b; 1975) have argued that we should reject this pessimistic view and continue our efforts to develop improved detoxification and rehabilitation procedures. While the search goes on for more effective ways to enable maintenance to achieve a

stable social adjustment, with abstinence following maintenance, such improve...ents have not yet been demonstrated.

Whether we can improve the outcomes following detoxification or not, we still do not have the evidence that maintenance is a treatment that can increase the probability of eventual abstinence. It may well decrease that probability even while it dramatically reduces opiate abuse and arrests for those who stay in treatment. Untreated addicts do sometimes become abstinent, though not with dramatic regularity. Maintenance treatment seems never to have attracted more than about 20 percent of a community's heroin addicts, but it may attract those who correctly perceive that they have a negligible probability of becoming abstinent. Therefore comparisons of treated to untreated addicts in self-selected groups have not given us the basis for an informed treatment policy, nor will they in the future.

Policy issues about maintenance duration can be discussed more clearly by distinguishing several types of treatment termination. The first is a disciplinary discharge for severely disruptive or dangerous behavior that threatens the integrity and effectiveness of the program for other patients. Behavior such as armed threats or dealing illicit drugs on the program premises clearly should not be tolerated, and discharge for these reasons cannot be weighed against therapeutic issues for the patient so discharged. However, this type of behavior is shown by only a very small fraction of patients. A second type of discharge results when a patient is sentenced to prison, where again no therapeutic issues are relevant except to detoxify the patient as humanely as possible in the time available. At the other extreme, a patient who has shown good social functioning and no opiate abuse for months or years may decide to terminate maintenance. Presumably one should allow such patients to attempt detoxification, while providing supportive help to make their prospect for success as good as possible. There seems to be reasonably good consensus in the field about these three types of termination, but altogether they account for a minority of terminations in most programs.

There is more controversy about three other groups of patients: those who do well but do not decide to terminate, those who are doing poorly but do choose to leave maintenance, and those who show continued opiate abuse and/or poor social functioning. For these three groups of patients clinical opinion ranges from a policy of strongly

encouraging continued maintenance to a policy of strongly encouraging or even requiring termination. It is my impression that the former policy is characteristic of programs with strong medical leadership and programs that are relatively insulated from community advocacy pressure, while the latter policy is more common in programs with strong paraprofessional leadership and programs that are subjected to antagonistic community advocacy pressure.

How can we form a policy regarding termination from maintenance treatment that will maximize treatment effectiveness? The major New York follow-up studies of terminated patients provide two relevant conclusions that bear on this question. The first is that patients who terminate before they have achieved stable social functioning are very unlikely to remain abstinent. The second is that even patients who terminate under the best of circumstances still may have less than a 50 percent chance of remaining abstinent as long as 3 years, and in some settings this probability seems to be much lower. Therefore it seems that well-functioning maintenance patients might be put in rather serious jeopardy if required to terminate. The McGlothlin and Anglin (1981a) study casts some doubt on the generality of this estimate of risk, but the circumstances in Bakersfield when its maintenance program was closed seem rather unique, and generalization seems impossible until we have additional research in this area. When treatment funding is reduced or many seemingly deserving applicants are knocking at the door, program staff seem more ready to force poorly functioning patients to detoxify. Some states have enacted regulations that require termination if opiate abuse continues after some period of time on maintenance. The justification for such a stance is a presumption that maintenance treatment is not helping such a patient, or at least is not helping that patient as much as it would help the typical applicant waiting to replace the person terminated. Unfortunately, we do not have direct evidence about the effectiveness of continued maintenance treatment among early poor performers. We all know of examples of poor performers who after a longer time were able to make great progress. Without more relevant evidence about the consequences of offering maintenance to a known poor performer versus an unknown applicant for treatment, the policymaker is in a quandry.

Clinicians feel an allegiance to the patients they know, in whom they may have invested great effort, and they will usually choose to retain current patients, or will at

least rationalize the extrusion of such patients as part of a confrontational treatment ideology that holds such a posture to be therapeutic. The McGlothlin and Anglin (1981b) comparison of three programs with different therapeutic ideologies seemed to suggest that a confrontational style in maintenance treatment is less effective than other approaches, but other program differences may have accounted for the observed differences in outcome. Dose levels may have been inadequate, or this particular program may have implemented this treatment style incompetently.

Administrators and elected officials who have little or no contact with patients may feel more directly the pressure of community demands for service to a broader group. At the same time they may not feel justified in funding program expansion. It is natural for such persons to raise the question of whether program funds would have greater community utility if poor performers were terminated and others given access to treatment. Without direct evidence about the consequences of these policy alternatives, rational choice is impeded and ideology expands to protect us from recognizing our ignorance.

A CLINICAL PERSPECTIVE

Having now carried on at length in the role of cautious scientist and critic, let me don briefly the hat of the clinician who must act rather than contemplate. What program policies should be adopted if one wants to utilize the research evidence about dosage and duration effects, while being sensitive to community opinion that dosage and duration should be minimized, being responsibly mindful of the limited availability of treatment funding and skilled staff, and not forgetting the large and continuing public problem presented by heroin addiction? I have a few suggestions for keeping one's balance on this multidimensional policy tightrope.

In treating the patient who is beginning maintenance for the first time, I would bring dosage up to a level of 40 to 60 mg within the first week or two. For 20 to 30 percent of new patients I would continue to increase dosage up to at least 80 mg by the end of the second month. The selection of this high dose group is still hard to specify with confidence. It would certainly not include patients who show no opiate positive urine tests after the second

week of maintenance. It probably should include patients who show schizoid or paranoid personality features or have a history of a psychiatric hospitalization that lasted more than 3 or 4 days. Uninterrupted opiate positives on weekly tests over the first 6 weeks might also be used as an indication to raise to at least 80 mg.

I would then use the third to perhaps the eighth month of maintenance as a period during which to observe the pattern of opiate abuse, discussing this with the patient, but in a supportive way and without applying any sanctions except to restrict take-home privileges. Whenever a patient showed 2 months with no more than one or two opiate positives, I would begin tapering to 40 mg, reducing no more rapidly than 5 mg every 2 weeks. Up to this point I would retain control over dosage and administer medication on a single blind basis, while informing patients of the overall treatment plan. When patients reached 40 mg and had been stable there for 2 months I would then ask them to regulate their own dosage, within some upper limit such as 80 mg.

Patients who show persistent heavy opiate abuse after the sixth month of maintenance I would then make the focus of special diagnostic and treatment attention. I would review the current usage and potential utility of adjunctive medication along the lines recommended by Kleber (this volume, part I, chapter 4). If vigorous complaints of "medication not holding" persist even when the patient abstains from heroin use for 1 or 2 weeks, I would explore the possibility that the patient is an individual who metabolizes methadone atypically. A trial on LAAM maintenance might be considered if LAAM has been approved for general use (or a switch to methadone if the patient is doing poorly on LAAM). Having reviewed these physiological and pharamacological issues, I would also initiate more vigorous psychosocial treatment interventions. These would depend on the patient's needs, the available staff time and skills, and the treatment philosophy of the program. Interventions might range from vigorous sanctions for continued opiate abuse to vigorous attempts to engage the patient and significant others in psychotherapeutic work.

The strategy of these early phases of treatment would thus be to reserve expensive psychosocial interventions for those patients who do not do well on an initial period of relatively inexpensive and unbureaucratic maintenance

treatment. I would aim to retain as many patients as possible during this first year.

After 1 year I would offer extended maintenance treatment indefinitely to any patients who can and will limit their use of opiates to a low level, regardless of how poorly they may be functioning in other areas of their life. For those who continue heavy opiate abuse, I would make maintenance contingent upon their engaging with some commitment in a continuing psychosocial treatment process aimed at reducing opiate abuse and improving areas of poor social functioning. Although only a small number of patients may be appropriate for an extended psychosocial adjunctive treatment, I do not believe that present program funding can support this additional treatment, nor attract or develop the skilled clinicians that it requires. Therefore it will need to be supported by patient fees or fee-for-service third party reimbursement. I would review patient progress relatively formally at about 12-month intervals. Those patients who had not met these conditions during the past year, either limiting their opiate abuse or remaining engaged in more intensive treatment, I would require to terminate maintenance.

In summary, I would seek to provide a program with a clearly visible and teachable treatment philosophy, yet one that still recognizes the wide range of patient needs. I would concentrate initially on a simple, inexpensive, unbureaucratic, pharmacologically oriented treatment that would be sufficient for a large group of patients. I would reserve the more complex and expensive psychosocial interventions for a more difficult group of patients, using contingent maintenance as an additional moderate incentive to improve treatment feasibility and continuity, with a relatively long time perspective for evaluating patient participation and progress. Finally, I would try to recognize, and to help my staff and patients recognize, that some patients who want to remain on maintenance treatment must be asked to yield their slot to others who may find it more helpful.

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CRITIQUE

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There is an aphorism that contrasts statistical significance with clinical significance: "A difference is not a difference unless it makes a difference." Or, as the biochemist Racker commented about some particularly meaningless data on radioactivity measurements: "Not everything that counts, counts."

Hargreaves' paper, to which we have the task of responding, is a thorough, careful, analytical, scholarly review on the dosage and duration questions. It calls proper attention to the requirements for valid research in this difficult field, especially the need for blind design. It shows how few of the published studies (including our own) even come close to meeting these requirements. It gives very high marks to the large-scale cooperative study by Ling et al. (1976). We agree with these assessments.

METHADONE DOSAGE

In one respect we agree even more strongly than Hargreaves agrees with himself, for we would discount completely all studies in which patients knew their dosages, or in which dosage groups were not formed by random assignment. The reasons for this categorical rejection are deeply rooted in design considerations pertaining to all clinical research. They are especially compelling in research on addicts, who consider themselves experts on self-medication, and for whom, therefore, an open dosage comparison defeats any possibility of examining effects of dosage per se.

But even with rspect to the 10 acceptable papers listed in his table 1, Hargreaves has overanalyzed the data. In his exhaustive microscopic examination of every tree, he has largely lost sight of the forest.

No one believed, in the light of knowledge about individual differences in pharmacokinetic and pharmacodynamic response to drugs, that there was one optimal dose of methadone suitable for all patients. One has to understand methadone dosage research in its historical context. The originators of methadone maintenance were guided by two

articles of faith never properly tested in rigorous clinical trials: first, that maintenance on dosages in excess of 100 mg daily were appropriate for most patients in order to provide a heroin "blockade" (Dole and Nyswander 1965); and second, that such maintenance, replacing some missing factor in a "metabolic disease," would usually have to be lifelong, as with insulin for diabetes (Dole and Nyswander 1967).

The early dosage experiments were designed to test whether such high doses for all patients were reasonable, or whether they were excessive for many patients. A general principle in clinical pharmacology, that the lowest dose that does the job is best, had not been tested for methadone.

It is interesting to read all those early blind dosage comparisons again, those of Jaffe (1971), Jaffe et al. (1969), Berry and Kuhn (1973), and the several studies with which Goldstein was associated (1971, 1972, 1973). They tell a clear and simple story if one avoids a myopic obsession with minor statistical and typographical errors. The findings, some of them surprising at the time, may be summarized as follows:

(a) Dosages much lower than previously employed seem to be no less effective in most patients with respect to the major outcome criteria -- heroin use, retention in treatment, and symptom complaints.

(b) Dosages in the 30-50 mg range seem to be marginally less effective; dosages of 50 mg and higher are essentially equivalent for most patients.

(c) Plasma levels, at a given dosage, vary widely, both with time in the same patients and between patients (Inturrisi and Verebely 1972; Horns et al. 1975). At maintenance dosages, plasma levels are no better a predictor of symptomatology than is dosage (Horns et al. 1975).

Our own assessment of the Ling et al. (1976) results is that although there was evidence of a statistically significant advantage of 100 mg over 50 mg, this advantage was rather small. It could all have been due, for example, to an earlier suppression of heroin use at the outset, following which a reduction to 50 mg might have been

as effective as further maintenance on 100 mg. Thus, we consider the dosage result in this study to be generally more in agreement than in disagreement with the earlier investigations.

The really striking result of this study was the very large outcome difference between clinics, a difference that far outweighed any advantage of one dosage level over another. It is interesting, in this connection, to note the following comment from Garbutt and Goldstein in 1972:

> In contrast to the unimportance of dosage within any given program, large differences may be observed between programs employing identical dosage schedules . . . . It is apparent that for most addicts, much more than methadone alone is required to achieve a change of life style, abstinence from illicit drugs, and social rehabilitation. Even on large doses of methadone, patients do not necessarily give up heroin use. The common complaints that "methadone is not holding me" and that "I need more methadone" evidently are not to be taken at face value but require skillful translation. When the staffs of methadone programs finally accept the fact that such complaints cannot be dealt with successfully by manipulating the methadone dose, effort can be directed more undistractedly toward the interpersonal transactions that are central to the task of rehabilitation.

Our subsequent 9 years of experience have not given us reason to change that statement.

The relative unimportance of dosage, provided some minimum is exceeded, is consistent with our knowledge about opiate pharmacology. For most drugs, there is indeed an ideal dosage "window" for each patient. A certain minimum dosage is needed, but toxicity ensues if the dosage is too high. What makes the opiates different is the facile development of tolerance. Indeed, if complete tolerance developed to all opiate effects, the physiological state of a patient maintained on 200 mg would be indistinguishable from that of a patient maintained on 50 mg. No acute opiate effects would be present in either patient, and both would have a high degree of cross-tolerance ("blockade") to heroin. The reality is somewhat different from this theoretical ideal, for tolerance develops more slowly and

less fully to some effects (e.g., constipation or suppression of sex hormone levels), and therefore excessive dosages may produce side effects despite the general level of tolerance.

Side effects at high methadone dosage have been documented. In a study on six patients maintained on methadone for 15 weeks, the last 8 weeks at a stable dose of 100 mg, Martin et al. (1973) noted a persistent decrease in blood pressure, pulse rate, and respiratory rate and an increase in rectal temperature. Hemodilution was found in all patients, with persistent edema in one. Subjectively and behaviorally, patients showed an increase in social withdrawal, lethargy, and hypochondriasis, and decreased motivation, efficiency, and sense of well-being. Sexual activity was decreased, and although partial tolerance developed, at the end of 15 weeks patients still complained about problems with potency and delayed ejaculation. Mendelson et al. (1975) reported significantly depressed levels of serum testosterone in methadone patients, especially those maintained on doses over 60 mg. Cicero et al. (1975) noted significantly reduced ejaculate volume, seminal vesicular and prostatic secretions, testosterone levels, and sperm motility in methadone patients; he found no correlation with dosage. In regard to the respiratory depressant effects of methadone, Santiago et al. (1977) found that the hypoxia-sensitive chemoreceptor mechanism never developed full tolerance to the acute effect of a methadone dose, even in subjects who had been on methadone for 8 to 43 months. Kreek (1973) reported increased sweating in 48 percent and persistent constipation in 17 percent of patients maintained on 80-120 mg for 3 or more years.

Our conclusion from all the blind studies is that a dosage in the 50-100 mg range (e.g., 80 mg) is suitable for most patients. This fact offers a simple, straightforward, authoritative, standard way of managing induction for all patients. For example, Goldstein and Judson (1973) followed such a standard induction schedule, bringing all patients to 80 mg by the 11th daily dose, then later testing the effects of slow dosage increase or decrease. Presumably, some patients will manage well on less, others may require more; but such individual differences in dosage requirements cannot be ascertained from group comparison data. This brings us to the heart of the matter. Given that different folks may require not only "different strokes" but also different dosages, is there a practical

method of individualizing maintenance dosages once patients have been stabilized on a standard dosage?

Several studies have shown the feasibility of allowing patients to know and adjust their dosages within reasonable limits (Angle et al. 1973; Goldstein et al. 1975; Havassy et al. 1979; Stitzer et al. 1979). Unfortunately, the validity of such a procedure is compromised by the "take-home" phenomenon. Although it is well known that some patients share or sell methadone that is placed in their possession (Stephens and Weppner 1973; Resnick 1977), there is no way to distinguish these patients from the others. A patient who wants extra methadone, above what it needed to be comfortable, has only to complain loudly and persistently of "feeling sick," or -- in some clinics -- to use heroin before urine tests to "prove" that the methadone dosage is inadequate.

Thus, placing a potent opiate in the hands of an opiate addict not only endangers the community and innocent members of the patient's family (Aronow et al. 1973; Smialek et al. 1977), not only impedes social rehabilitation by making the patient a potential source of drugs for others, but also makes medically proper dosage adjustments virtually impossible.

A solution to the dosage problem is LAAM. In all reported trials, this long-acting surrogate opiate has proven to be as safe and efficacious as methadone (Ling et al. 1976; Jaffe and Senay 1971; Zaks et al. 1972; Senay et al. 1977; Marcovici et al. 1981; Goldstein and Judson 1974), and it is preferred by patients, too (Trueblood et al. 1978). With thrice-weekly dispensing, and "take-home" restricted to a very select group of patients who have proved their reliability over a long time, it should be possible to allow dosage self-adjustment within wide limits. Why, then, is LAAM not in general use? We shall return to that question later.

Duration of Surrogate Opiate Maintenance

Is there an optimal duration of surrogate opiate maintenance? We doubt that any feasible experiment could be devised to answer this question. It is instructive to examine why, because the case is so typical of the limitations of research in the field of addiction. It goes without saying that merely comparing programs committed to

long-term retention with those committed to early termination could not possibly yield a useful answer. There would be too many uncontrolled variables -- geography, ethnic composition, staffing and staff attitudes, ancillary services, and background of the patients with respect to addiction history. We observed, as have most investigators, that the earliest patients to enter a new program do much better on all criteria than the later cohorts do. Thus, even within the same program, concurrent comparison of randomly constituted groups is the only way to obtain valid data for any comparison of treatments.

Now, suppose one did compose randomly assigned and well matched groups. What then? If patients knew at the start whether their group was destined for short-term or long-term treatment, this knowledge would probably outweigh the very variables one wished to test. Is the solution, then, to keep the assignments blind, until one day, without warning, patients assigned to short-term maintenance are detoxified and sent on their way? Even if informed consent could be obtained for such a bizarre procedure, the different times of termination for different patients, depending on the start dates, would be a serious problem. Imagine the morale in such a program, in which, week after week, regardless of circumstances and without warning, some patients are suddenly terminated, while others who entered at the same time continue in treatment.

It is well recognized that some problems -- in the laboratory as well as in the clinic -- are simply not amenable to proper experimental study, whether by reason of technical, fiscal, or ethical limitations. However, this does not prevent us from using our common sense and best humane clinical judgment in deciding what to do. We propose two simple premises about surrogate opiate maintenance, which, in our opinion, lead inescapably to four conclusions about policy:

> Premise 1: The principal goals in the use of surrogate opiates are (in decreasing order of importance) to help opiate addicts give up their addiction to illicit opiates, become rehabilitated in society, and eventually, if possible, give up their dependence on the surrogate opiate.
>
> Premise 2: It is better to be maintained on a surrogate opiate than to be addicted to heroin.

Conclusion 1: Patients should be encouraged to detoxify from surrogate opiate maintenance, and to try abstinence when, in their own opinion, concurred in by staff, they have made sufficient rehabilitative progress.

Conclusion 2: Patients should be assisted in detoxifying if they insist, even against staff advice, and regardless of staff assumptions about their likelihood of success.,

Conclusion 3: Patients should never be compelled to detoxify against their wishes, except for disciplinary reasons when the program will be jeopardized by their retention in treatment.

Conclusion 4: Former patients who relapse to heroin use after a drug-free period should be able to return, on demand, without delay, and without impediments being placed in their way, for further surrogate opiate treatment.

Conclusion

Thus, our general conclusion is that there should be no policy on treatment duration, other than to provide both surrogate opiate and support services when and as often as they are required, and detoxification at the patient's request. Translated into a working model, this would mean that there should be in each community a multimodality treatment program ready to offer multiple services -- counseling, detoxification, drug-free alternatives, surrogate opiate maintenance, and antagonist maintenance -- at all times for all addicts, whatever their previous histories may be, and regardless of how many times they have cycled through treatment programs in the past.

REGULATION IMPLICATIONS

It seems appropriate, at this time in our national political history, to ask whether in the field of addiction treatment, as in other spheres of activity, governmental regulation has been overdone.

We add our voices to those of Dole and Nyswander (1976), Senay et al. (1981), and others, in asking that the treatment of addicts be returned to its proper place as a medical endeavor; that physicians and ancillary health personnel be allowed to treat addicts according to the state of the art and to their best medical judgment; and that intrusive and counterproductive regulatory interventions by Federal, State, and local governmental agencies be terminated.

In our opinion, the only justification for governmental intervention in the treatment process is to protect the community from exposure to potent narcotics distributed by the treatment clinics. But curiously, despite the excessive zeal of the regulatory bureaucracies, this one necessary regulation has never been enacted.

The general adoption of LAAM, with its three-times-a-week dispensing schedule, would make it possible to eliminate the dispensing of "take-home" opiates -- except for those who are well along the road to complete rehabilitation -- without imposing undue hardships. This would also dramatically improve the therapeutic environment in programs employing surrogate opiates. Yet FDA approval of LAAM for this restricted use remains bogged down in a Kafkaesque tangle of delays. But who really cares? LAAM won't earn a profit for anyone. And the patients LAAM could help are powerless outcasts. Rehabilitating heroin addicts is no longer a popular enterprise, the welfare of addicts is of little interest to the bureaucrats, and the addicts have no politically effective constituency to plead their cause.

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DISCUSSION SUMMARY

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Everyone agreed that there is considerable evidence that higher dose levels of methadone improve retention, especially early in treatment, and result in lower levels of illicit opiate use. In particular it was agreed that the best designed dose study, the VA collaborative research study, demonstrated some superiority of the higher (100 mg) dose, although there were significant variations among programs on the effects of dose. It was suggested that the rate of dosage change may be as important as the absolute dosage level, a rapid achievement of the maintenance dose being desirable. (Increases in dosage should not exceed the degree of tolerance developed by the individual, i.e., no acute effects such as euphoria or sedation should be experienced.) Some participants believed that once a patient was stabilized on a maintenance dose, factors other than dose were more important in determining treatment retention.

There was general agreement that dose level should be individualized empirically. For the majority of patients the most effective doses will be between 50 and 100 mg. Because of the data indicating some superiority of higher doses, it was thought that higher doses should be used when clinically indicated, even over 100 mg per day if required. Dr. Kreek noted that when other drugs such as rifampin or phenytoin, which affect the uptake or metabolism of methadone or its derivatives, must be used, it may be essential to increase the methadone dose above 100 mg. In the discussion it was noted that in many programs the average daily dose is being reduced below 50 mg. Some programs are even adopting a 30 mg dose as the dose of choice. Such standard dosing policies were considered to be inappropriate by all participants.

There was some discussion about the correlation between dose, plasma level, and outcome. It was noted that none of these variables correlate strongly. This lack of correlation may be due to a number of different variables and complex interactions, e.g., plasma protein binding, opiate receptor binding, distribution, etc. Although all agreed it would be helpful if a therapeutic window could be determined, because of the above-mentioned lack of correlation, most of the participants expressed little optimism.

Most of the participants believed that some patients could be permitted to regulate their own dose provided that: (1) the clinic staff monitored the dosage changes to ensure that self-adjustment is not abused; (2) the clinic staff provided consultation to the patients on dosage changes; and (3) there was a limit on the frequency of dosage change. Dr. Goldstein was not opposed to this concept on medical grounds but objected because of the potential for diversion. Dr. Kleber was of the opinion that at least a substantial minority of patients attempt to use dosage increases to deal with anxiety and other symptoms in ways which tend to perpetuate drug-seeking behavior. Consequently, he recommended that requests for dosage adjustment should be handled by first determining if there are any underlying problems which should be treated, rather than automatically granting a dose increase. Dr. Kreek noted that the final decision about any dosage changes must be made by a physician but the decision should be responsive to the patient's needs and requests.

There was concurrence that the research findings indicate that patient performance (measured by drug use, employment, and criminality) is much better while the patient is in treatment. The majority also agreed that the data strongly suggested that the longer the duration of treatment the more likely a positive outcome would be sustained following treatment. There was unanimous agreement that these findings had the following implications for treatment:

1. The decision to detoxify from methadone maintenance treatment should be made by the patient's physician in conjunction with the patient and other staff. No restriction should be placed on duration of maintenance treatment. Patients detoxified from methadone maintenance should be readmitted upon request.

2. No single methadone dose is best for all patients. The dose should be individualized for each patient. In most cases a dose of 100 mg or less will be sufficient; however, under certain circumstances higher doses will be required.

The participants agreed that in view of the limited funding, additional dose studies are not currently warranted because (1) considerable data are already available with respect to dose and outcome, and (2) the relationship

between dose and outcome is sufficiently complex that further studies are unlikely to rapidly produce definitive results.

CHAPTER 3. FACTORS MODIFYING THE PHARMACOLOGICAL EFFECTIVENESS OF METHADONE

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There are many diverse factors which may, in theory, significantly modify the pharmacological effectiveness of methadone. However, only a few of these factors have been delineated by carefully controlled clinical studies. Some further studies are in progress or have been proposed, and clearly many more are needed since significant alterations in the pharmacological effectiveness of methadone can lessen or negate the therapeutic utility of such treatment. In medicine and in clinical therapeutics in general, only recently has it been widely recognized that factors such as chronic disease and drug interactions may alter drug disposition and thus drug action.

Three types of factors which have been demonstrated to significantly modify the disposition of methadone, and thus potentially its pharmacological effectiveness, will be discussed. These include: 1) chronic diseases, including chronic liver disease, chronic renal disease, and possibly other diseases; 2) drug interactions, including interactions of methadone with rifampin and phenytoin in man, possibly with ethanol and disulfiram, and also, by inference from animal studies, interactions of methadone with phenobarbital, diazepam, desipramine, and other drugs, as well as with estrogen steroids; and 3) altered physiological states, in particular, pregnancy. Modifications of pharmacological effectiveness of methadone in man by some of these factors has been demonstrated dramatically by clinical signs and symptoms; in other instances the alterations are more subtle.

Another type of factor which might modify the pharmacological effectiveness of methadone would be factors which alter receptor binding or subsequent responses to methadone at receptor sites. Other than studies of interactions of methadone with specific narcotic antagonists, such as naloxone, or naltrexone, there are no clinical studies to date suggesting such alterations (Kreek 1973b; Kreek 1976b). However, the recent provocative report

that, in vitro, alcohol selectively inhibits binding of enkephalins to opiate receptors of the delta class suggests that some agents also might be able to prevent binding of exogenous opioids to specific or to all classes of opiate receptors (Hiller et al. 1981). This may be due to alterations in membrane fluidity caused by ethanol (Chin and Goldstein 1977).

Chronic liver disease is the most common medical problem in both heroin addicts and methadone-maintained patients (Cherubin 1967; Louria et al. 1967; Sapira et al. 1968; Jersild et al. 1970; Kreek 1972; Kreek et al. 1972; Cherubin et al. 1972a; Cherubin et al. 1972b; Stimmel et al. 1972a; Stimmel et al. 1972b; Stimmel et al. 1973; Kreek 1973a; Cherubin et al. 1976; Webster et al. 1977; Kreek 1978a; Kreek 1981b; Novick et al. 1981a, b; Kreek and Hartman 1982). In many reports including retrospective and carefully controlled prospective studies, it has been shown that around 50-60 percent of all heroin addicts entering methadone-maintenance treatment have biochemical evidence of chronic liver disease, and that over 50 percent of patients in chronic methadone treatment have persistent liver abnormalities. At the same time, it has been shown that methadone itself is not hepatotoxic; patients with normal liver function at time of admission to methadone treatment do not develop abnormalities of liver function, except when they are chronic alcohol abusers or when they contract acute viral hepatitis. Clinically, the chronic liver dysfunction observed may be asymptomatic or may be accompanied by mild, moderate, or severe signs and clinical symptoms. Chronic hepatic dysfunction observed in methadone-maintained patients is primarily of two etiologic types: 1) sequelae of earlier acute infection with hepatitis B virus or one of non-A non-B viruses which may include chronic persistent hepatitis, chronic active hepatitis, and post necrotic cirrhosis; 2) alcohol-induced liver disease including fatty liver, alcoholic hepatitis, and alcohol cirrhosis; and also 3) mixed types of diseases (Kreek 1972; Kreek et al. 1972; Kreek 1973a; Kreek 1978a; Beverly et al. 1979; Novick et al. 1981b). It has been shown that 10-12 percent of adult and also adolescent methadone-maintained patients are chronic carriers of the hepatitis B antigen (or virus) and around 50 percent have hepatitis B core antibody. Recently in a study of maintained patients with chronic liver disease, it was shown that 96 percent have some marker of prior hepatitis B infection. The percentage of patients with chronic sequelae due to hepatitis non-A non-B viruses is unknown.

In prospective studies of methadone-maintained patients, it was shown that around 20 percent of patients were using an excessively large amount of alcohol while still taking heroin, and that around 25-35 percent of adults and adolescent methadone maintained patients are persistent chronic abusers of alcohol. In this group, progressive liver disease may be anticipated (Kreek 1972; Kreek et al. 1972; Kreek 1973a; Kreek 1978a; Beverly et al. 1979; Kreek 1981a; Kreek 1981b; Novick et al. 1981b; Hartman et al. 1983).

In various studies it has been shown that the liver may play a central role in several aspects of methadone disposition, including not only methadone metabolism and clearance but also storage and subsequent release of unchanged methadone (Kreek et al. 1978). Thus the liver may serve a reservoir function. Studies carried out in rats have shown that unchanged methadone persists in the liver for up to 6 weeks after administration of a single dose (Harte et al. 1976). In studies performed using the isolated rabbit liver, it has been shown that methadone is avidly extracted from portal venous blood in a single pass through the liver after a bolus injection into a non-recirculating perfusion system (Kreek et al. 1978). Over 85 percent of a bolus of methadone is taken up by the liver, as contrasted with only 25 percent of a bolus of morphine in a single pass in this system. The subcellular distribution of methadone is also significantly different than that of morphine. Methadone is primarily found in fractions containing nuclei and membranes, whereas morphine is primarily found in the cytosol. In these studies it was shown that methadone is slowly released in unchanged form from the liver into the effluent blood (Kreek et al. 1978).

Over the past few years, it has been recognized that the response of liver disease may significantly alter the disposition of several drugs. The profound importance of these findings has prompted the performance of increasing numbers of studies to determine the various effects of different types and degrees of severity of liver disease on disposition of specific drugs. An initial study of methadone disposition, without use of radio-labeled or stable-labeled isotope tracer techniques, has been carried out in maintenance patients with mild, moderate, and moderately severe chronic liver disease, including patients with compensated cirrhosis. Fourteen patients with biopsy documented liver disease and five otherwise healthy methadone-maintained patients have been studied (Novick et

al. 1981a). The patients have been classified into subgroups according to the severity of liver disease based on clinical and biochemical data as well as biopsy diagnosis. Plasma levels of methadone were determined at specific time points following oral administration of usual daily doses of methadone. Methadone disposition was significantly altered only in the subgroup of five patients with moderately severe but compensated cirrhosis. Four of these patients had jaundice or ascites. Although 1) mean area under the plasma concentration time-curve was higher, 2) mean plasma concentration was higher, and 3) apparent oral clearance was lower in this group than in five otherwise healthy patients, these differences in pharmacokinetics and disposition of methadone were not significant. However, the mean plasma apparent terminal halflife of methadone was significantly prolonged in patients with compensated cirrhosis as compared with otherwise healthy contrast subjects.

One study has been performed to determine the amounts of methadone and its metabolites excreted in urine of patients with chronic liver disease as contrasted with otherwise healthy maintained patients (Kreek et al. 1980a). To perform this study a method was developed for the simultaneous quantitation of methadone and six of its major and minor pharmacological active and inactive metabolites using chemical ionization mass-spectrometry with direct probe introduction of samples to increase sensitivity. The total 24-hour urinary excretion of methadone and its metabolites was 48.3 percent (±1.7 SEM) in otherwise healthy patients, but was significantly lower, 31.6 percent (±3.19 SEM) in patients with chronic liver disease ($p < 0.05$). The total 24-hour excretion of the pyrrolidone metabolite, the end product of two pathways of methadone metabolism, was also significantly reduced in patients with liver disease. Similar methods now have been developed to determine the amounts of methadone and its metabolites in feces, and these methods are being used to complete balance studies of methadone disposition in patients with chronic liver disease as contrasted with otherwise healthy patients.

Further significant abnormalities in methadone disposition in maintained patients with mild to moderately severe chronic liver disease may be delineated in studies now in progress in which stable isotope tracer techniques are being used (Hachey et al. 1977; Kreek et al. 1979a). These techniques permit the measurement of the fate of a single dose of methadone during chronic treatment. Also

using these techniques, the fate of the separate enantiomers of methadone can be determined. In a pilot sequence of studies, carried out using one stable isotope species, pentadeutero-methadone, with separate administration of each labeled enantiomer as well as of the racemic form, it was shown that the plasma disappearance and urinary excretion of the active l (-R-) enantiomer of methadone was slower than that of the inactive d (-S-) enantiomer in maintained patients (Kreek et al. 1979a). A new technique for the simultaneous stereoselective kinetic studies of methadone enantiomers has been developed, using three deuterium labeled forms of methadone, coupled with gas liquid chromatography-chemical ionization mass spectrometry (Nakamura et al. 1982). (This technique will allow the determination of the fate of the active and inactive enantiomers of methadone simultaneously as well as the effects of administration of each of these enantiomers on the body stores of unlabeled compound in patients with liver disease as well as in otherwise healthy subjects.)

Although other studies have suggested that in addition to having alterations in drug disposition, patients with liver disease may have increased cerebral sensitivity to sedative and analgesic drugs, none of the patients in any of these studies had any clinical evidence of increased cerebral sensitivity to methadone, probably because of the development of a high degree of tolerance to narcotics. However, it is not known whether or not the rate of development of tolerance to methadone is significantly different in patients with chronic liver disease who are being inducted into methadone treatment. It is also not known whether the persistence of methadone during and following detoxification is prolonged in this group of patients. Finally, no studies of methadone disposition and effects have been conducted in patients with severe or uncompensated chronic liver disease, or in acute fulminant forms of liver disease. Very severe liver disease or abrupt changes in hepatic status in patients with these conditions may cause significant alterations in methadone disposition with concomitant clinical symptoms.

To facilitate proper selection and subgroup classification of patients with chronic liver disease, a new liver function test, the stable-isotope-labeled ^{13}C-aminopyrine breath test, has been modified and validated in methadone-maintained patients (Kreek et al. 1981b). In this test a single dose of stable-labeled substrate is administered

orally, and the hepatic handling of this compound is assessed by measurement of exhaled stable-labeled carbon dioxide. This test now has been shown to be an excellent diagnostic tool to detect the presence of cirrhosis, compensated or uncompensated, in methadone-maintained patients as well as in unmedicated patients. This noninvasive test may be used to identify cirrhosis, when the use of a liver biopsy is not possible because of medical contraindications, ethical considerations, or lack of patient acceptance. This stable labeled test may be repeated several times if needed and may also be used in women of childbearing potential.

Elevations in plasma proteins of all types are observed in methadone-maintained patients. These may be due in part to chronic liver disease and in part to a past history of chronic injection of foreign substance, as well as other possible factors. Of greatest interest has been the findings of elevations in levels of serum albumin in many patients in this population, which has a high prevalence of chronic liver disease as well as chronic alcohol abuse. Normal, as well as occasional elevated levels of serum albumin, with infrequent decreased levels of serum albumin, have been observed in restrospective and prospective studies of adult patients on methadone maintenance and also in studies of adolescent methadone-maintained patients (Kreek 1972; Kreek et al. 1972; Kreek 1973a; Kreek 1978a; Hartman et al. 1983). Similar observations have been made in a special study of chronic alcoholic methadone-maintained patients (Kreek 1981a). There is no precedent for such findings of persistent elevations in serum albumin levels. Studies carried out in rabbits have shown that chronic administration of methadone results in an apparent sustained increased synthesis of albumin coupled with accelerated degradation (Rothschild et al. 1976). Increased intravascular as well as extravascular amounts of albumin have been observed in these studies (Rothschild et al. 1976). It has been shown that methadone is bound to albumin, acid glycoprotein (α-1 globulin), α-2 globulin, and other globulin fractions (Olsen 1972; Olsen 1973; Olsen 1975; Tocque et al. 1980; Romach et al. 1981). To date there has been no evidence that there are significant alterations in methadone disposition due to any fluctuations in plasma protein binding, although this is possible, and to date only minor fluctuations in total plasma protein binding of methadone have been observed in maintained patients with or without liver disease, since methadone binds to multiple plasma proteins.

Disposition and action of many drugs are significantly altered by chronic severe renal disease, especially when excretion in urine is the major pathway of elimination of drug and its metabolites. There is essentially no information concerning any possible modification of the pharmacological effectiveness of methadone in patients with renal disease and only one pilot study of methadone disposition in such patients. Methadone disposition was studied in three maintained patients with chronic renal disease including one oliguric patient undergoing peritoneal dialysis, one anuric patient on hemodialysis, and one patient following renal transplantation (Kreek et al. 1980b). In these patients there was neither laboratory nor clinical evidence for accumulation of methadone and its metabolites. In all three patients plasma levels of methadone remained within the appropriate therapeutic range (0.09 to 0.68 μg/ml) for the doses received (50-60 mg/day). It was shown that less than 1 percent of the daily dose of methadone was removed by either peritoneal or hemodialysis. Of great interest was the fact that in one anuric patient, it was found that the administered dose of methadone and its metabolites were excreted exclusively by the fecal route. Clearly, further studies of the effects of chronic renal disease on methadone disposition and resultant alterations in pharmacological effectiveness of methadone in that population are needed.

The clinical efficacy of methadone has been shown to be significantly altered in man by two major pharmacological agents, the antituberculosis drug, rifampin, and the anticonvulsant drug, phenytoin (or Dilantin).

Rifampin was initially introduced for treatment to resistant strain and far advanced tuberculosis, and remains the drug of choice in these settings. More recently, it has gained widespread favor as the drug of choice for treatment of tuberculosis. Several years ago, shortly after the introduction of rifampin, several methadone-maintained patients complained of the abrupt onset of withdrawal symptoms within a few days after rifampin was added to their therapeutic regimens. A relationship between the onset of abstinence symptoms and rifampin was not recognized in the first few patients, most of whom began using illicit narcotics to self-medicate the symptoms. One of those earlier patients soon left methadone treatment because of abstinence symptoms and weeks later died of a drug-related overdose. However, in a special clinic for combined treatment of tuberculosis and methadone, where the patients were well known by their physicians and the

rest of the clinic staff, the question of significant interaction between rifampin and methadone was soon raised when patients consistently complained of abstinence symptoms. Twenty-one of 30 methadone-maintained patients in this special clinic developed mild to severe narcotic withdrawal symptoms when rifampin was added to their therapeutic regimens. These symptoms would begin each day 6-8 hours after the combined methadone rifampin treatment was given and would last until 1 or 2 hours after methadone was given on the following day. Special studies were carried out in six patients who developed severe symptoms but who at the same time needed rifampin treatment for their tuberculosis (Kreek et al. 1976a). Plasma, urine, and fecal levels of methadone and urine, and fecal levels of the major pyrrolidine metabolite were determined by gas liquid chromatography techniques. Each patient served as his own control with studies carried out both while receiving methadone plus rifampin and also while receiving methadone alone. During concomitant rifampin treatment plasma methadone concentrations were consistently and significantly lower at each time point after oral methadone dosing.

Urinary excretion of pyrrolidine, the major metabolite of methadone, increased 150 percent during rifampin treatment. In those patients from whom 24-hour fecal collections could be obtained, fecal excretion of the major pyrrolidine metabolite was significantly increased during concomitant rifampin treatment. The two observed effects of rifampin on methadone metabolism, i.e., a lowering of plasma levels of methadone coupled with increased urine and fecal excretion of the major N-demethylated pyrrolidine metabolite, support the formulation that methadone enhanced hepatic miscrosomal drug metabolizing enzyme activities. These significant alterations in methadone disposition were accompanied by the appearance of narcotic withdrawal symptoms in patients who had been previously well maintained on stabilized doses of methadone.

A second clinically important drug interaction with methadone has recently been documented. In several clinical observations it was noted that signs and symptoms of narcotic withdrawal developed within 2-3 days after initiation of phenytoin treatment for seizures (Finelli 1976; Tong et al. 1981). A study was carried out in methadone-maintained volunteers to determine the effects of phenytoin on the pharmacokinetics and pharamacological action of methadone (Tong et al. 1981). Each methadone-maintained volunteer was studied before, during, and after

concomitant phenytoin treatment. Plasma and urine levels of methadone and urine levels of the pyrrolidine metabolite were determined by gas liquid chromatography. The mean area under the methadone-plasma-concentration time curve was significantly decreased during concomitant phenytoin administration. The ratio of the major pyrrolidine metabolite to unchanged methadone excreted in urine increased significantly during phenytoin treatment. Each of the volunteers studied developed moderately severe signs and symptoms of narcotic withdrawal within 3-4 days of beginning phenytoin in therapeutic doses. The timing of onset of symptoms and the findings of altered metabolism of methadone without significant changes in total plasma protein binding suggest that the mechanism involved in this drug interaction is not due to displacement of protein binding of methadone, but rather due to enhanced metabolism of methadone during phenytoin administration. Methadone-maintained patients requiring phenytoin should be observed carefully for signs and symptoms of methadone withdrawal and may require increases of methadone doses or alterations in dosing schedules.

Alcohol is used to excess by 20-50 percent of methadone-maintained patients (Kreek 1978b; Kreek 1981a; Kreek 1981b). Alcohol abuse is also common in adolescent former heroin addicts in methadone treatment. In an ongoing study it has been shown that around 20 percent of these young patients are heavy users of ethanol, consuming a mean of around a 17-ounce equivalent of whiskey each day (Kreek 1981a). At the same time, in both the study of young patients as well as in another prospective study of adult methadone patients, it has been found that over 40 percent of such patients remain in chronic methadone maintenance for 3 years or more with successful treatment judged by cessation of illicit narcotic use, even though heavy alcohol use continued. In methadone-maintained patients, two types of anecdotes have been reported with respect to effects of alcohol: 1) that large amounts of alcohol "boost the methadone effect"; and 2) that during chronic heavy use of alcohol early abstinence, i.e., withdrawal symptoms prior to the end of the 24-hour dosing interval for methadone, is observed (Kreek 1978b; Beverly et al. 1979; Kreek 1981a; Kreek 1981b). In studies of interactions of some other drugs with ethanol, primarily carried out using animal models, it has been shown that ethanol has a biphasic effect on drug metabolism. When ethanol is present in large amounts, drug metabolism is inhibited, yet when ethanol is no longer present, following chronic administration of large amounts of this agent,

drug metabolism is accelerated, apparently due to the enhancement of hepatic microsomal drug metabolizing enzyme activities. In one study carried out in rats it was shown that on the day following chronic administration of both methadone and ethanol, plasma levels of methadone were lower following the daily dose than they were in animals treated on a chronic basis with methadone alone (Kreek 1981). In another study, it is shown in rats that administration of a single dose of methadone resulted in lower levels of methadone in brain and liver following chronic treatment with ethanol than in control animals (Borowsky and Lieber 1978). However, in an *in vitro* study, it has been shown that ethanol does not prevent the hepatic uptake of methadone (Kreek et al. 1981a).

One study of the effects of acute ingestion of modest amounts of ethanol, such as may be consumed in a social setting on methadone disposition, was performed and no significant effects observed (Cushman et al. 1978). Studies of possible interactions of clinical significance between ethanol and methadone in methadone-maintained patients who are alcohol abusers have been initiated. Such studies are potentially of great importance because of the magnitude of the clinical problems of alcohol abuse in the methadone-maintained population.

Possible effects of chronic methadone treatment on ethanol elimination have been carried out in the rat (Wendell and Kreek 1979; Kreek 1981a). It has been well established by many investigators that during chronic treatment with ethanol, ethanol elimination becomes accelerated; this is the so-called "adaptive increase." However, the mechanisms underlying these effects of ethanol on its own metabolism remain in controversy. Studies have been carried out to determine the effects of chronic methadone treatment on ethanol elimination in the rat model. Animals were first stabilized on chronic treatment with either methadone or sham treatment with vehicle alone, and then each group subdivided with continuation of methadone or vehicle treatment along with ethanol or isocaloric sucrose administered by liquid diet for 3 weeks. Pair feeding was used throughout these studies. Ingestion of ethanol exceeded 20 g/kg/day. At the end of these studies, the weights of animals in all groups were similar. Ethanol elmination was studied on the final study day. Chronic treatment with methadone alone caused an acceleration in ethanol disappearance rates which were significantly higher than the accelerated elimination rates observed in animals treated on a chronic basis with ethanol. Combined

ethanol and methadone treatment resulted in a significant further acceleration in the rate of ethanol elimination. Thus, apparently methadone-affected ethanol elimination is by a mechanism different than that underlying the "adaptive increase" in ethanol elimination which occurs during chronic ethanol administration. Because of the findings of this study, in the ongoing studies in humans, possible effects of methadone on ethanol elimination are being assessed in addition to the effects of chronic ethanol administration on methadone disposition.

Disulfiram (Antabuse) is the only pharmacological agent which has been shown to date to have significant deterrent effects on recidivism following detoxification from ethanol. A study has been carried out in volunteer methadone-maintained patients who are not chronic heavy users of alcohol to determine possible interactions between methadone and disulfiram. Therapeutic doses of disulfiram (500 mg/day) were administered orally for 7 days to seven volunteer subjects, and plasma and urine levels of methadone along with urine levels of the pyrrolidine and pyrrolidine metabolites were measured. Systematic assessment of subjective signs and symptoms of possible narcotic intoxication or abstinence before and during disulfiram administration was carried out. Although the mean plasma levels of methadone were lower during concomitant disulfiram administration, these levels were not significantly different than the methadone levels observed during methadone treatment alone.

However, the ratio of urinary excretion of methadone to its major pyrrolidine metabolite was significantly lowered during concomitant disulfiram administration. Also the urinary excretion of the pyrrolidine metabolite increased relative to the excretion of methadone during the disulfiram treatment. These findings suggest that the N-demethylation of methadone may be enhanced during disulfiram administration rather than inhibited as postulated at the beginning of the study. In this short-term study in volunteers, disulfiram had no apparent effects on the clinical status of patients since no symptoms of narcotic overdose or of narcotic withdrawal were experienced. Clearly, longer-term studies of possible interactions of significance between disulfiram and methadone in maintenance patients who are former heavy users of alcohol, but who desire chronic disulfiram treatment, are needed.

Other dispositional interactions between methadone and specific drugs have been described in animal models, but

to date there have been no confirmatory studies in man. Using the rat as an experimental animal, significant dispositional interactions between methadone and phenobarbital, methadone and diazepam, methadone and desipramine, as well as methadone and ethinyl estradiol have been described (Alvares and Kappas 1972; Spaulding et al. 1974; Roerig et al. 1975; Liu and Wang 1975; Kreek 1976b; Kreek 1978b; Kreek et al. 1979b; Kreek 1981b). Each of these interactions is provocative and worthy of appropriate study in man. It should be reemphasized that animal models alone are not sufficient to delineate potentially clinically significant drug interactions with methadone, because methadone disposition, including pharmacokinetics, metabolism, and routes of excretion, is significantly different in animals than in man (Kreek 1979). For instance, whereas the plasma disappearance halflife of methadone in man is determined to be around 24 hours if no tracer techniques are used, and around 36-48 hours when stable isotope tracer methods are employed (Kreek 1973b; Kreek et al. 1979a; Nakamura et al. 1982), in the rat, during chronic methadone treatment, the apparent terminal halflife of methadone is around 90 mm (Kreek 1979). A similar short plasma halflife of methadone has been observed in the mouse (Burstein et al. 1980). Thus, although animal studies may be helpful in the identification of possible drug interactions of significance, results from such studies must be interpreted with caution, especially with respect to any attempts to extrapolate the findings to man. Animal studies may serve as a helpful prelude to the more difficult to perform controlled clinical research studies in man. However, appropriate use of animal models as well as various in vitro preparations may be essential to delineate the mechanisms underlying specific drug interactions with methadone.

The third type of factor which may alter the pharmacological effectiveness of methadone is that of altered physiological states. There have been many clinical anecdotes that during pregnancy the effectiveness of methadone seems to be reduced, even when the dose of methadone is held constant. Frequently, this problem is compounded by the common practice of reduction in methadone doses in late pregnancy. A pilot study of methadone disposition during pregnancy has been completed. Three patients who were maintained on constant doses of methadone during the second half of pregnancy were studied. Plasma levels of methadone were found to become progressively lower during the third trimester of pregnancy. This lowering of plasma levels of methadone with resultant decreased areas under

the plasma concentration time curves could not be explained by increased weight or increased body water alone. Also preliminary findings have shown that any minor fluctuations in binding of methadone to plasma proteins during late pregnancy do not account for all the changes in plasma levels of methadone observed. Thus, these findings have suggested that methadone metabolism may be altered in late pregnancy possibly due to a predominant effect of progestins on hepatic drug metabolism in that setting. Because of these very provocative findings from this study, a more extensive study of methadone disposition during the third trimester of pregnancy and in the postpartum period is now in progress.

In summary, several specific factors have been delineated which significantly alter the pharmacological effectiveness of methadone during chronic treatment (see table 1). These include chronic liver disease as well as possibly chronic renal disease, drug interactions with methadone including interactions of methadone with rifampin and phenytoin, as well as possibly other interactions with drugs and hormones, and also altered physiological state of late pregnancy.

There are several immediate needs related to factors which may modify the pharmacological effectiveness of methadone. These needs include: 1) dissemination of well documented information now available from various completed research efforts; 2) extensive further basic clinical research studies in man in controlled settings to extend existing information obtained in pilot studies to determine if findings obtained in animal studies pertain in man and to perform studies of new possibly modifying factors; and 3) some further studies in animals and in vitro models, primarily for the elucidation of mechanisms observed modifying factors. Such further research and resultant information is critically needed to improve the overall efficacy of chronic methadone maintenance treatment.

Table 1. Factors modifying pharmacological effectiveness of methadone

I.	Chronic diseases		
		A.	Chronic liver disease (postviral; alcoholic)
			1. Mild to moderately severe
			2. Severe; compensated or uncompensated
		B.	Chronic renal disease -- severe (?)[1]
		C.	Other (?)[1]
II.	Drug interactions with methadone		
		A.	Rifampin
		B.	Phenytoin
		C.	Ethanol (? man)[2]
		D.	Disulfiram
		E.	Phenobarbital (? man)[2]
		F.	Diazepam (? man)[2]
		G.	Desipramine (? man)[2]
		H.	Estrogen ? (? man)[2]
		I.	Other
III.	Altered physiological states		
		A.	Pregnancy
		B.	Other (?)[1]

[1](?) Suspected but not experimentally documented.
[2](? man) Documented experimentally in animal models but not yet in man.

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CRITIQUE

Edward Senay, M.D.

Dr. Kreek has covered the literature on factors modifying the pharmacologic effectiveness of methadone, but has not mentioned other factors not covered in literature but which clinical experience would mark for investigation. I have minor questions concerning Dr. Kreek's review of the effects of chronic liver disease. First, the rate of occurrence of liver disease in heroin addicts applying for treatment cited by Dr. Kreek at 50-60 percent appears to be low. In the Illinois program the rate is closer to 90 percent, and other authors have found similarly high rates. Dr. Kreek properly notes that what is impressive about the liver findings in addicts is their apparent lack of clinical significance. Her review of studies of the chronic liver disease, which I think might be more appropriately termed persisting indications of liver disease without clinical expression, appears to offer further evidence that the set of biochemical abnormalities noted in chronic addicts does not have much clinical significance.

Similarly, renal disease does not appear to be associated with clinically significant alterations of methadone biotransformation.

Dr. Kreek advances pharmacologic data demonstrating that rifampin and phenytoin both speed the metabolism of methadone to a degree which is clinically relevant. I agree with Dr. Kreek that one of NIDA's priorities should be to disseminate information to the field concerning these effects.

The drug-drug interaction of the greatest possible significance is that between alcohol and methadone. Dr. Kreek cites two clinical observations: a) that of the "boosting effect" of alcohol on the intoxicating or potentially intoxicating effects of methadone; and b) the observation that acute consumption of high amounts of alcohol appears to speed the biotransformation of methadone. Of all the relationships we could study, this latter relatinship is most deserving of study because it appears to be the most frequently relevant clinical interaction. Dr. Kreek's review of the scientific data indicates that methadone and alcohol appear to speed metabolism of each other in reciprocal fashion; thus pharmacologic factors may account for

heavy drinking of alcohol in methadone maintenance patients.

My clinical experience to the effect that disulfiram does not appear to have clinically significant side effects when used in methadone maintenance patients is confirmed by Dr. Kreek's review of this relationship. We do not have data concerning long-term consequences of concurrent administration of methadone and disulfiram; I would give such a study a fairly high priority in view of the multiple drug use pattern which now seems to be prevalent in our population.

I can only agree that studies of methadone disposition are urgently needed in pregnancy. The dilemma presented by a pregnant opioid dependent woman is important from a public health viewpoint and should be studied much more intensively than it has been to date. In addition to its possible clinical utility, a study of the biotransformation of methadone in neonates might add substantially to our knowledge. There would appear to be more variation in the opioid withdrawal syndrome in the neonate than in the adult. Presumably immaturity of the enzyme systems which are responsible for the biotransformation of opioids underlies the variation.

Dr. Kreek does not mention two other physiologic events that appear, on clinical grounds, to alter the disposition of methadone in man. One is the apparent effect of sudden large changes in temperature. In the clinic, one has experiences with stabilized "good" patients, apparently not playing the "I want more methadone" game, who will report withdrawal symptoms in association with a large change in temperature in either direction. Similar reports also appear when a previously sedentary patient begins a job which is demanding physically. These are two naturally occurring phenomena which could be studied.

Finally, we have the intriguing question of emotional stress on methadone disposition. In NIDA's research agenda, study of this relationship might well have medium to high priority, for on clinical grounds, such factors would appear to be important on a daily basis.

DISCUSSION SUMMARY

James R. Cooper, M.D., Fred Altman, Ph.D., and Kim Keeley, M.D.

The discussion focused on factors which modify the plasma levels of methadone and thus the potential physiological effects of the drug. The effects of alcohol, other drugs, pregnancy, and even such diverse factors as brussel sprouts, flu vaccine, and illness, were mentioned in this regard. Highly significant lowering of the plasma levels of methadone during the third trimester of pregnancy has been documented, which cannot be explained on the basis of weight gain or changes in plasma protein binding by albumen or gamma globulin fractions alone. The only drugs specifically identified as affecting plasma level in man sufficiently (reduction of up to 50 percent) to require additional methadone were phenytoin and rifampin. Methadone doses must usually be increased for a few days until the patient adjusts to the drug interaction effect.

Special attention was given to methadone patients who are chronic users of alcohol. Dr. Kreek presented some information from her ongoing research on such patients. In a few patients studied to date, after chronic ingestion of large amounts of alcohol a biphasic change in plasma methadone levels was observed; higher than usual plasma levels of methadone were found for a few hours after ethanol ingestion, which is attributed to inhibition of drug metabolism by alcohol, followed by a downward plunge to lower than usual levels of methadone, which is attributed to microsomal induction. Following the next dose of methadone the cycle was repeated if alcohol was again ingested. If alcohol was not ingested, plasma levels of methadone remained lower than usual until the effects of prior chronic ethanol use on microsomal drug metabolizing enzyme activities had disappeared.

There was considerable discussion about the halflife of methadone. Dr. Kreek presented some of her recent work using stable isotope labeled methadone. She described a multiphasic curve of the disposition of methadone with the final phase having a halflife of over 2 weeks in adults receiving chronic methadone treatment. In a study of neonates born to methadone-maintained mothers it was shown that the methadone halflife was approximately 2 days, as evidenced by the disappearance of methadone in urine (without the use of stable isotope labeled methadone).

It was noted that for a wide range of plasma levels there appears to be no correlation with withdrawal signs and/or opiate craving. At very low levels of plasma methadone and when there are rapid changes in plasma level over the 24-hour dosing interval, such signs and symptoms do occur. There seems to be a better correlation between dose and effect than between plasma level and effect. The fact that 90 percent of plasma methadone is protein bound and that the volume of distribution is large, were mentioned as possible explanations of this finding. There was considerable discussion about the need for further development and utilization of techniques for assessing plasma levels.

CHAPTER 4. CONCOMITANT USE OF METHADONE WITH OTHER PSYCHOACTIVE DRUGS IN THE TREATMENT OF OPIATE ADDICTS WITH OTHER DSM-III DIAGNOSES

Herbert D. Kleber, M.D.

INTRODUCTION

For the heroin addict, drugs are both a way of life and a way of coping with life. Opiates produce euphoria, banish despair, and provide oblivion. Because of these effects, therapists have been reluctant to continue any more than necessary the patient's dependence on drugs during treatment.

Physicians in methadone programs have already accepted the principle, by use of methadone, that it is appropriate to prescribe some drugs in the treatment of the narcotic addict. In carrying out the remainder of treatment, however, they usually wish to diminish the patient's reliance on drugs to solve all of life's problems. Trying to stick to this belief, they find themselves on the one hand under pressure by patients seeking drugs, especially minor tranquilizers, or on the other hand, wanting themselves to prescribe something because they believe that patients could benefit from use of a particular drug such as an antidepressant or antipsychotic agent.

Their problem is made more difficult by relatively few controlled studies about the use of psychotropic drugs in the treatment of narcotic addicts; the lack, until recently, of adequate tools for accurate diagnostic assessment; pressure of time and too many patients; and, finally, the pressure by other staff, who want the physician either to prescribe no other drugs, or to prescribe drugs that will in some almost magical way solve the patient's problems.

There has been more chaos than consensus concerning the incidence and prevalence of various psychiatric disorders or symptom clusters in drug addicts. Confusing the picture even more is the effect of methadone on any underlying emotional problems. Does methadone lead to depression

or improve it? Does it suppress the symptoms of schizophrenia to some degree or worsen such symptoms? The presentation of psychopathology by patients maintained on methadone may be quite different from that when the same patient is on a very low dose or when not on methadone. At times, immediately following withdrawal, there seems to be emergence of symptomatology even where the detoxification has been slow and stress has been minimal. Symptoms of psychosis or mania have been observed under such circumstances. This paper will look at what is currently known about the use of psychotropic drugs in the treatment of methadone-maintained patients, including indications and contraindications for use, and what further studies need to be done.

Psychiatric Disorders in Opiate Addicts

Before discussing the drugs in question, it is important to have a picture of the prevalence of psychiatric disorders in these patients. Although there have been a number of studies of psychopathology in addicts, most have usually employed only dimensional symptom or personality scales. Diagnostic techniques, especially the recently improved ones, have not usually been used in this population. A major recent exception has been the large-scale study recently completed at Yale by Kleber et al. (1981). Psychiatric diagnosis was obtained on 533 subjects applying for treatment at the multimodality Drug Dependence Unit of the Connecticut Mental Health Center in New Haven, Connecticut. (An additional 107 addicts who had not applied for treatment were also located and studied, but will not be described here.) The 533 broke down as follows (Rounsaville et al. 1982a):

1. A pilot sample of 157 subjects (149 of whom were evaluated using the Research Diagnostic Criteria (RDC)) was evaluated at the Screening and Evaluation section, and represents a group that was seen as they were applying for treatment. One hundred seven of these 157 subjects were evaluated on a catch-as-catch-can basis, and the remaining 50 subjects were consecutive admissions to treatment.

2. A sample of 204 additional consecutive admissions at the Screening and Evaluation Unit were interviewed following the completion of the pilot sample.

3. One hundred twenty subjects were members of the Methadone-Maintenance Program who were evaluated at least 3 months after being taken into the program. Sampling in this treatment program was on a catch-as-catch-can basis.

4. Sixty subjects were Hispanics who were evaluated in Spanish and were evaluated on application to treatment (N=30) or after entering a residential therapeutic community for Hispanic patients (N=30).

Subjects in all populations surveyed were paid for participating in the study and were interviewed only after informed written consent was obtained. All subjects in this study met Research Diagnostic Criteria for narcotic dependence, which are as follows: withdrawal as shown by four or more of the following symptoms appearing within 24 hours of cessation of the drug -- insomnia, sweating, flushing, runny nose, chills, stomach cramps, diarrhea, muscle pain, nausea, gooseflesh, or twitching; or daily or near daily use of illicit narcotics for more than 2 weeks; or participation in a methadone program for 3 weeks or more; or use of illicit narcotics 3 or more days per week for more than a month.

Diagnostic Techniques

Information for making diagnostic judgments was collected on the Schedule for Affective Disorders and Schizophrenia (SADS). On the basis of the information collected on the SADS, the subjects were classified on the Research Diagnostic Criteria (RDC), which are a set of operational diagnostic definitions with specific inclusion and exclusion criteria for a variety of nosologic groups.

Diagnoses on the RDC are made both for the current time period (point prevalence rates) and for a lifetime (lifetime prevalence), except for several diagnoses which are considered lifetime diagnoses only, whether or not the subject is currently manifesting symptoms. These lifetime diagnoses are the labile, cyclothymic, and antisocial personality disorders, Briquet's syndrome, and bipolar disorders. Psychiatric disorders are categorized as "other" if they cannot be categorized into any of the diagnostic criteria specified in the RDC because of limited information or absence of diagnostic criteria for the particular set of symptoms.

Table 1 shows the current rates of psychiatric disorders. Using the SADS-L, diagnoses are made for both the current time period and for a lifetime. Depression is the most commonly diagnosed symptomatic condition, as 23.8 percent of the sample were in a current episode of major depression at this evaluation. Other affective disorders, including minor depression (2.3 percent), manic disorders (0 percent), and hypomanic disorders (.9 percent) were comparatively infrequently diagnosed, as were schizophrenia (.2 percent) and schizoaffective disorders (1.5 percent). Only small fractions of the sample were in current episodes of panic (.9 percent), obsessive compulsive (1.3 percent), or generalized anxiety (.9 percent) disorders. However, a substantial minority had a current phobia (9.2 percent) or abused alcohol to a degree that met the criteria for a current episode of alcoholism (13.7 percent).

Table 2 shows the lifetime RDC diagnoses. It shows that 86.9 percent of the addicts surveyed met the criteria for some psychiatric disorder exclusive of drug addiction in their lifetime.

Looking at the lifetime rates of specific disorders, the most commonly diagnosed disorders were major depression (53.9 percent), alcoholism (34.5 percent), antisocial personality (26.5 percent), intermittent depression (18.8 percent), labile personality (16.5 percent), phobic disorder (9.6 percent), schizotypal features (8.4 percent), minor depression (8.4 percent), other psychiatric disorders (6.8 percent), hypomanic disorder (6.6 percent), and generalized anxiety disorder (5.4 percent). All other disorders, including schizophrenia, schizoaffective disorders, mania, cyclothymic personality, obsessive compulsive disorder, panic disorder, and Briquet's disorder were found in less than 5 percent of the sample. When affective disorders are combined, it is apparent that opiate addicts in this sample are at high risk, in that 74.3 percent met the criteria for some affective disorder.

Multiple Diagnoses

RDC diagnoses are not mutually exclusive and multiple diagnoses were common in our sample. To evaluate the presence of multiple diagnoses, similar categories were grouped so that six types of disorders were defined: depressive/dysphoric disorders (major depression, minor depression, intermittent depression, labile personality, cyclothymic personality), manic disorders (mania hypomanic

Table 1. Current rates/100 of psychiatric disorders in opiate addicts according to research diagnostic criteria N=533

Current RDC Diagnosis	N	Rates/100
Affective Disorders		
Major depression	127	23.8
Minor depression	12	2.3
Manic disorder	0	0.0
Hypomanic disorder	5	0.9
Schizophrenia	1	0.2
Schizoaffective Disorders (depressed and manic)	8	1.5
Anxiety Disorders		
Panic	5	0.9
Obsessive compulsive	7	1.3
Generalized anxiety	5	0.9
Phobic	49	9.2
Alcoholism	73	13.7
Other Psychiatric Disorder	25	4.7
Any Current Disorder (including personality diagnoses)	375	70.3

Table 2. Lifetime rates/100 RDC psychiatric diagnoses in addicts by sociodemographic characteristics
N=533

Type of Disorder	Percentage
Affective Disorders	
Major depression	53.9
Minor depression	8.4
Intermittent depression	18.8
Cyclothymic personality	3.6
Labile personality	16.5
Manic disorder	.6
Hypomanic disorder	6.6
Bipolar 1 or 2	5.4
Any affective disorder	74.3
Schizophrenic Disorders	
Schizophrenia	.8
Schizoaffective depression	1.7
Schizoaffective manic	.4
Anxiety Disorders	
Panic	1.3
Obsessive compulsive	1.9
Generalized anxiety	5.4
Phobic	9.6
Any Anxiety Disorder	16.1
Alcoholism	34.5
Personality Disorder	
Antisocial personality	26.5
Briquet's	.2
Schizotypal features	8.4
Other Psychiatric Disorders	6.8
Any Lifetime Disorder	86.9

disorder), schizophrenic disorders (schizophrenia, schizoaffective disorder, depressed and manic), anxiety disorders (obsessive compulsive, generalized anxiety, panic, phobic), alcoholism, and personality disorders (antisocial, Briquet's, schizotypal features). Using this system, 13 percent had no disorders, 35 percent had one category of disorder, 31 percent had two, 16 percent had three, and 5 percent had four or five.

SCHIZOPHRENIC DISORDERS

The incidence of psychosis, usually schizophrenic reactions, in opiate addicts has been estimated from as low as 1 percent (Valliant 1966) to as high as 19 percent (Gerard and Kornetsky 1955). The recent Yale study puts the combined figure for schizophrenic and schizoaffective disorders at less than 2 percent. The relation of opiate drug use to psychosis has been a mixed and confusing picture throughout the past 200 years. Whereas some authors saw morphine as a useful treatment for psychotic disorders and other psychiatric problems (Carlson and Simpson 1963; Comfort 1977), others saw its chronic use as a cause of such psychosis (Bell 1911), a view disputed by still others who could not find such an effect (Pfeffer and Ruble 1946; Kolb 1925). The recent discovery of opiate receptors and endogenous opiate-like substances has increased our knowledge but not solved this particular problem. Some researchers find opiate agonists to exert an antipsychotic effect (Berger et al. 1980) while others find that, on the contrary, antagonists have such an action (Gunne et al. 1977). Still others find that neither agonists or antagonists have a consistent effect (Wikler 1952; Janowsky et al. 1977).

Antipsychotic medications block dopamine receptors and stimulate prolactin secretion (Langer et al. 1977). Methadone (Gold et al. 1977) and morphine (Gold et al. 1978) have also been shown to increase serum prolactin, suggesting that an antipsychotic effect may be indicated by opiate agonists stimulating opiate receptors in the brain to modify dopamine impulse flow and release, interfering with the postsynaptic action of dopamine (Gold et al. 1978). However, Judd et al. (1981), attempting to test this by giving single doses of methadone to schizophrenic patients, found that while there was an increase in serum prolactin, the schizophrenic symptoms were not improved and, in fact, there was an accentuation of emotional withdrawal and decreased motor activity. Since multiple doses

may be needed to establish an antipsychotic response and/or to induce tolerance to the narcotic sedative effect, the experiment is in no way conclusive. A single case study, for example, by Berken et al. (1978) showed a dramatic effect on schizophrenic rage by prolonged treatment with methadone.

Watson et al. (1979) have reviewed the contradictory and conflicting theories and findings relating to opiate peptides and schizophrenia, and they proposed a possible solution:

> It is likely that the several opiate peptide systems and the multiple opiate receptors described earlier, may have different pharmacological susceptibilities...certain opiate receptors are only weakly responsive to morphine or naloxone-like agents and require considerably higher doses to be affected. Furthermore, endogenous opioids have been shown to require higher doses of antagonists for their blockade. To explore the opiate psychosis problem, it may be necessary to characterize the other classes of opiate receptors and to use agents directed at them....

While there may be disagreement on the relationship of exogenous opiates, endogenous opiate-like substances, opiate antagonists, and opiate receptors on the signs and symptoms of schizophrenia, it seems that methadone alone may be insufficient to treat the disorder as it appears in maintained patients. Thus, there is general clinical agreement that it is useful to use the major tranquilizers in treating such patients (Kleber and Gold 1978; Ciccone et al. 1980; Kaufman 1974; Chappel 1974; Ferris 1976). No particular drug stands out in this context; chlorpromazine, thiothexene, fluphenazine, and haloperidol are all mentioned. It has also been pointed out that lower doses of such drugs may be needed in these patients to control psychotic symptoms (Kleber and Gold 1978; Ciccone et al. 1980), perhaps because methadone either potentiates their effects or has its own antipsychotic action.

Although schizophrenic patients may be no more common in methadone programs than in the general population, when they are present they may present special problems in handling (Salzman et al. 1973) and may have difficulties with the strict structure and limit-setting present in many programs. The relation of opiates and endogenous

opiate-like substances to schizophrenic symptoms is controversial, but the use of the neuroleptics to treat such symptoms in methadone patients is not. In general, these drugs should be used cautiously because of the possibility of tardive dyskinesia; lower doses than normal can often be employed. Unlike some of the other categories of psychotropic drugs discussed in this paper, these drugs are usually not abused by addicts, and the problem more often is getting the patients to continue on them when they are indicated.

MINOR TRANQUILIZERS IN THE TREATMENT OF ANXIETY DISORDERS

The data from the Yale study indicate that approximately 10 percent of their opiate addicts were diagnosed as having an anxiety disorder. It has been noted by a number of authors that diazepam has become a popular drug of abuse among opiate addicts and in methadone programs (Kleber and Gold 1978; Woody et al. 1975a, b; Gould et al. 1977; Budd et al. 1979; Spensley 1976). Approximately 20 percent of urines have been reported to contain diazepam in Los Angeles methadone clinics (Budd et al. 1979). The question therefore arises whether this use is an attempt to treat anxiety and should be viewed as self-medication, or whether it represents another way of getting high. Diazepam is said to "boost the high" experienced after methadone, preferably using 25-50 mg of the tranquilizer (Kleber and Gold 1978), or to produce "a pleasant, relaxed sensation which may be described as a 'high'" (Woody et al. 1975a, b).

Such patients are frequently noted to appear sleepy, ataxic, and dysarthric at the methadone clinic and occasionally to have pathological rage attacks (Kleber and Gold 1978). There have been no controlled studies reported in the literature using diazepam or other benzodiazepines to treat anxiety in opiate addicts or methadone patients, with the exception of Sugarman et al. (1971), who used prazepam to treat anxiety in detoxified narcotic addicts. Although it was better than a placebo in reducing anxiety during the first 2 weeks of treatment, by the third week there was no longer an advantage.

A number of possibilities exist to explain the interaction between diazepam and methadone. Diazepam could interfere with the normal metabolism of methadone and thereby produce a methadone-induced euphoria. This possibility is

supported by Spaulding et al. (1974) with methadone-dependent rats. Diazepam, by augmenting GABA-ergic transmission in the central nervous system (Keller et al. 1976), could augment effects of opiate agonists at catecholamine nuclei and pathways, causing mood, motor, and aggressive changes seen in patients abusing diazepam while on methadone. Evidence from animal studies may support a potentiation of opiate agonist effects by diazepam (Shannon et al. 1976), but the neurochemical mechanism by which this interaction occurs remains to be defined. One additional possibility, suggested by studies of blocked and unblocked heroin administration which demonstrate the marked antianxiety effects of opiate agonists, is the clinical experience of seeing detoxifying addicts use large amounts of diazepam to ameliorate detoxification. The explanation, based on the previously mentioned possibility that diazepam boosts the opiate high, would be that diazepam modified endorphin binding or release to stimulate endogenous opioid receptors involved in euphoria. This possibility could be evaluated by studies of naloxone-blocked and unblocked diazepam administration (Kleber and Gold 1978).

Although benzodiazepines have been shown in numerous controlled studies to be useful in treating anxiety in nonaddict patients, the problem in this population is whether the abuse potential outweighs the clinical usefulness. The abuse potential in methadone patients may be greater than in alcoholics (Kryspin-Exner and Demel 1975). There has also been increased attention of late to the problems of diazepam withdrawal even at lower doses than frequently used by methadone patients (Winokur et al. 1980). Under these circumstances it appears prudent to treat anxiety by counseling, training in relaxation techniques, or environmental manipulation rather than tranquilizers. One should also be cautious about treating anxiety by raising methadone dosage, often requested by patients if diazepam is refused, since any relief so gained is often short-lived and followed soon by a new request for a higher dose. Occasionally, when other methods have been unsucessful and the clinician is convinced of the presence of a serious anxiety disorder, diazepam may be used if care is exercised. Potential misuse is suggested by requested refill of prescriptions earlier than due, supposedly lost prescriptions, requests for increasing doses, and the desire for indefinite use (Spensley 1976). Even more clear-cut is the patient appearing excessively sedated or ataxic at the clinic. When misuse occurs, it should be considered that the dangers of the

drug now outweigh its usefulness, and prescriptions should be terminated. The patient, however, needs to be evaluated at that point as to the need for possible diazepam withdrawal and the decision made about the location for providing such treatment.

TRICYCLIC ANTIDEPRESSANTS IN THE TREATMENT OF AFFECTIVE DISORDERS

A number of studies have emphasized the incidence of depression in opiate addicts (Dorus and Senay 1980; Lehman and DeAngelis 1972; Robins 1974; Rounsaville et al. 1979; Steer and Kotzker 1980; Wieland and Sola 1970; Weissman et al. 1976), a finding consistent with the clinical theories of Wurmser (1974) and Khantzian (1977), who suggest that a main problem for the typical addict is regulation of affect and vulnerability to dysphoria. In the recent Yale study (Rounsaville et al. 1982b), approximately 24 percent of their sample were diagnosed as having a current major depression while over two-thirds were noted to have either chronic or episodic depressive disorders.

The efficacy of both pharmacotherapy and psychological treatments in depressive disorders has been demonstrated in several recent controlled clinical trials (Weissman 1979). Unfortunately, there are few such trials with methadone patients.

Spensley (1974) reported an uncontrolled trial of doxepin in 27 patients maintained on methadone whose target symptoms were: anxiety, depression, pseudo-withdrawal, sleeplessness, and apprehension. Twenty-five of 27 (93 percent) reported beneficial results of slight-to-marked degree. Similar findings were noted in five patients who received amitriptyline for the same type of symptoms occurring during voluntary withdrawal.

Woody et al. (1975c) conducted a double blind study of doxepin in 35 "mildly depressed patients" on methadone maintenance. Here diagnosis of depression was made by a psychiatric interview, and a number of depression-rating scales were also obtained, including the Beck, Zung, and Hamilton. Although dropout from the study was high (only 16 were on drug or placebo for longer than 4 weeks), there was statistically significant improvement noted for the doxepin-treated subjects as compared to the controls. Also the doxepin patients tended to be less likely to drop out. Improvement was found in symptoms of depression and

anxiety as well as in craving for heroin. There was also a significant decrease in amphetamine use in the doxepin group as compared to placebo-treated subjects.

In order to overcome these design limitations in the Woody study, a study was done in New Haven beginning in 1977 (Kleber et al., in preparation). To avoid the high Philadelphia dropout rate and also to avoid confounding results by the increasing doses of methadone and early program adjustment, the patient was stabilized on methadone before beginning imipramine. This latter drug was chosen instead of amitryptiline or doxepin partially because the sedating tricyclics have been abused by drug addicts in some cities (Stimmel et al. 1978; Cohen et al. 1978), but not all (Senay et al. 1977). Analysis of the data from the study initially seemed not to confirm the Woody findings, in that there was no significant difference between the drug and placebo group. Closer examination of the data revealed that this was due not to failure of the drug group to improve but rather to the major improvement shown by the placebo group, which did about as well as the doxepin patients in the Woody study. This can illustrate the variability of the depressive symptoms over time, the role of nonpharmacologic factors on outcome of depression, and, finally, the importance of not rushing in to use drugs to treat depression in these patients.

The tendency of depression present in the early stages of methadone treatment to improve significantly over time without other pharmacologic intervention has been stressed by two recent studies, one by Dorus and Senay (1980), and the other by Rounsaville et al. (1982b). Dorus and Senay suggest that "...a large portion of the elevated depressive symptomatology noted at intake is the result of an acute life stress situation.... Methadone treatment often results in a rapid reduction or cessation of heroin use and a dramatic change in a patient's lifestyle. This rapid treatment effect would be consistent with the rapid change in symptom level." Another recent study also showed some similar changes in methadone patients over time (Steer and Kotzker 1980).

Not explained by this theory, however, is the work by Mirin et al. (1976) showing that chronic opiate use (heroin in this case) results in increased feelings of dysphoria and depression. Even though plasma level or dose of methadone were not found to correlate with depression in one study (Blake and Distasio 1973), in another it

was noted that both antidepressants and methadone increase levels of 2-phenylethylamine (PEA), an endogenous amine structurally and pharmacologically similar to amphetamine. During and after detoxification from methadone, levels of PEA were noted to drop and depressive symptoms to rise (Inwang et al. 1975/76). These authors suggest that individuals with a low capacity to synthesize biogenic amines may become narcotic addicts in an attempt to self-medicate a biological tendency toward affective disorder. It may be, therefore, that the effects of chronic methadone use on noradrenergic transmission are the crucial variables that lead to remission of depression rather than programmatic or therapy variables. In general, however, the biological effects of narcotics are contradictory and remain to be further elucidated. Woody and Blaine (1979) have recently reviewed this as well as other theories of depression in addicts.

The New Haven study demonstrated that although the depressive symptoms often abated over time, those patients who were diagnosed as having a current major or minor depressive disorder at admission were more likely to use illicit drugs during the next 6-month period. It may be, therefore, that a subgroup of depressed patients could benefit from pharmacotherapy, but further study would be required before this point could be made with any conviction. In any event, tricyclic antidepressants could be considered for those patients who do not experience remission over the 3-6 months post-admission. The possibility of different subgroups requiring different treatments is strengthened by Schildkraut et al. (1976) and Meyer et al. (1978), who found that during heroin administration only four of nine patients showed elevated MHPG excretion. The abuse of stimulants such as cocaine (Stimmel et al. 1978) and methylphenidate (Raskind and Bradford 1975) by some methadone patients might be a signal that these are patients who are self-medicating depression and could benefit from tricyclic therapy.

There is agreement on the high incidence of current and past affective disorders in opiate addicts and methadone-maintained patients. There is less agreement over what to do about this finding and even less agreement as to whether the cause is psychological, psychosocial, or biological. Since there appears to be substantial change in depressive symptoms during the first 6 months on methadone without specific pharmacotherapy, it is probably best not to intervene with drug therapy until it is seen whether

spontaneous remission will occur. Tricyclic antidepressant medication should be considered for those patients who do not improve after 3-6 months or those abusing stimulants who may be trying to self-medicate. Current diagnostic techniques such as the SADS/RDC or DSM-III (Rounsaville et al. 1980) and symptom rating scales such as the Beck Depression Inventory have been shown to be useful in assessing depression in methadone patients and should be employed prior to beginning pharmacotherapy. For programs with limited psychiatric staff, the Beck Depression Inventory (either the 13-item (Beck et al. 1974) or five-item (Mintz et al. 1979 version) would be a useful screening tool to indicate which patients should then be more intensively evaluated.

MAO INHIBITORS

The stimulant properties of MAO inhibitors may have some abuse potential. Shopsin and Kline (1976) note that "amphetamine-like effects including euphoria, hypomania..., flight of ideas, and outward hostility can be associated with the use of all MAO inhibitors even in the usually prescribed dosage range for treating depression." The mechanism of action for this is not completely clear even though it is known that these agents, like the amphetamines, increase the available amount of norepinephrine, dopamine, and serotonin at synapses. Because of the abuse potential and risk of serious reactions when certain medications or tyramine-containing foods are used while individuals are on MAO inhibitors, dangers of use outweigh therapeutic potential in a drug-abusing population which can be notoriously careless with drug, alcohol, and food intake.

LITHIUM

The Yale study did not turn up any current patients diagnosed as manic, but found 0.9 percent hypomanic. In their lifetime, rates showed 0.6 percent manic, 6.6 percent hypomanic disorder, 5.4 percent bipolar 1 or 2, and 0.4 percent schizoaffective manic. Thus, there may be a significant number of patients for whom lithium might be a useful treatment or prophylactic agent.

While the efficacy of lithium carbonate in the treatment of bipolar affective illness is well established, the mechanism by which lithium exerts its therapeutic effects

remains to be determined. Byck (1976) has proposed the hypothesis that endogenous substances with opioid activity are inextricably involved in drug-induced, naturally occurring, and pathological bipolar euphoric states. On the basis of the effect of lithium on the binding of endorphins to opioid receptor sites (Snyder and Simantox 1977), Byck hypothesized that lithium interacts with a modified opiate receptor binding as if it were an opiate antagonist to prevent or modify drug-induced and pathological euphoric states. However, unlike the opiate antagonist naloxone, which blocks the euphoriant effect of morphine, lithium does not (Jasinski et al. 1977). Further, lithium has been reported to produce analgesia in man (Sxirmai and Sachs 1974) and to potentiate opiate agonist actions in rodents (Jensen 1974). In addition, lithium (Judd et al. 1977), as well as chronic opiate agonist administration (Mirin et al. 1976), can produce dysphoria and a feeling of sluggishness in man. Therefore, while there is theoretical support for the hypothesis that lithium exerts its therapeutic antieuphoric and antimanic action (Byck 1976; Belluzzi and Stein 1977) by modification of endorphin binding, it is unclear whether lithium exerts its long-term effect by potentiating or blocking opioid agonists or by other yet to be defined mechanisms.

Apparently Scher (1975) was the first to suggest treating narcotic addicts with lithium. He noted that lithium given to heroin addicts was associated with alleviation of withdrawal symptoms and blocking of heroin's euphorogenic effect. Altamura (1975), on the theory that drug addiction may be due to masked depression, gave lithium to 20 detoxified opiate (mainly heroin) addicts. While a few of the patients reported an enhanced feeling of well being on the drug and lessened psychological dependence, only nine patients took the lithium for more than a few weeks. Followup in general was poor, and the author concluded he could neither confirm nor refute his hypothesis. After 1 year, all patients were off the lithium and most were back on heroin.

Cronson and Cadden (1976) gave lithium to 11 addicts and felt that nine had an excellent response, with five remaining drug free after 2 years. Cronson (1979) later claimed that of 20 patients given lithium for at least 1 month, 16 substantially benefited. Flemenbaum (1974) hypothesized that a significant number of depressed patients and chemically dependent ones "share a common depressive oral personality but some express it as a clear affective disorder and some express it as parapsychiatric

symptoms that are usually conducive to sociopathy and/or chemical dependence." He felt that lithium might therefore be of help in treating such patients. In a later theoretical paper, however, where he elaborated on this theory (Flemenbaum et al. 1979), he concluded that results to date in regard to lithium's beneficial effect on opiate use are controversial and further demonstration is needed both at the animal and human level.

Kleber and Gold (1978) noted that methadone patients given lithium tended to ask for lower methadone doses because of increased drowsiness and that this occurred regardless of whether they felt they were helped by the lithium or not. These authors gave lithium to seven patients with a history of recurrent depression on the theory that narcotics might be blocking or attenuating the manic phase so that the true bipolar nature of their illness may not be apparent. Four of the seven patients noted clinical improvement of their depressive episodes while on the lithium. The authors review and speculate on possible theoretical mechanisms for such findings relating to neurotransmitter theory. Nahunek et al. (1978) report giving lithium to 23 "analgesic abusers" with equivocal results: 11 defined as satisfactory outcome; 12 as unsatisfactory. Better results were experienced with stimulant abusers.

There are a number of theoretical possibilities relating to the existence of undiagnosed or masked bipolar affective disorders in opiate addicts or the existence of atypical depression which could be helped by the use of lithium. Unfortunately, human studies to date have been small, uncontrolled, and at best inconclusive. Wider use of lithium in a few selected methadone programs might be encouraged so as to gain more clinical experience with combining the two modalities and to focus more clearly on the types of patients that may be helped. If clinical experience indicates sufficient usefulness, blind clinical trials can then be undertaken. The side effects of the combined usage, however, may make such blind trials difficult to carry out. Since lithium appears to be an effective agent in the treatment of the manic phase of manic-depressive illness and in the prophylaxis of both mania and depression in nonopiate patients, its use in methadone programs may lead to improved outcomes for a number of patients.

ALCOHOLISM AND THE USE OF DISULFIRAM

Abuse of alcohol by patients maintained on methadone has been recognized as a serious problem since the early 1970s. Until recently, however, there was disagreement as to whether the alcohol problems began while on methadone, or were due to it (for instance, as an alternative way to get high since heroin use was blocked), or preceded program entrance. There has also been confusion as to the extent of the problem since many studies failed to provide operational definitions of such categories as "excessive use of alcohol," "problem drinking," "alcohol abuser," or "alcoholism." An excellent review of these studies has been done by Carroll et al. (1977). Their review looks at numbers as well as theories about the combined use, and they conclude that most individuals who had trouble while on a program appear to have had previous problems with alcohol. Gelb et al. (1978) report that in 68 percent of methadone patients admitted for alcohol detoxification, their regular alcohol abuse preceded narcotic use, and 29 percent began their abuse after entering methadone-maintenance treatment. Green et al. (1978) studied 96 methadone patients chosen at random from a program in a predominantly white, lower middle class area. Using careful operationally defined criteria for their definitions of "alcoholic," "problem drinker," etc., they found a lifetime prevalence of excessive drinking of 26 percent and a current rate of 11 percent. Of patients with histories of heavy drinking, 72 percent had begun their abuse prior to the onset of opiate dependence. Their rate of heavy drinking during methadone maintenance was somewhat higher than during their active heroin use (42 percent vs 32 percent). Rounsaville et al. (1982a) found a similar rate of current alcoholism, 14 percent, in the Yale study of methadone patients. Other studies have ranged from 12 percent to 25 percent (Gerston et al. 1977).

Theories as to why some methadone patients abuse alcohol tend to fall into two categories: one stresses underlying psychiatric and psychosocial adjustment problems; the other focuses on a "generic hunger for a high" created by the patients' inability to get high on heroin while on methadone. Carroll et al. (1977) suggest, "These two explanations are not antagonistic. In fact, they are complementary, and we suspect they are both valid partial explanations for this phenomenon." Identification of patients with potential alcohol problems early in their methadone career may be helpful, and a modified self-

administered alcoholism screening test (SAAST) has been reported to be very useful in this regard (Cohen et al. 1977).

Alcohol abuse is associated with major physical problems, such as cirrhosis of the liver, and with premature death. In combination with methadone, overdose death can occur. In one study, 60 percent of the deaths in patients enrolled in or recently discharged from a methadone-maintenance program were alcohol related (Gerston et al. 1977). Also, it is a major cause of administrative discharge from such programs (25 percent in one study), and such patients often deteriorate rapidly after leaving. To cope with these problems, some programs send their patients to separate alcoholism treatment units while others try to treat them in the methadone program itself. Both approaches appear approximately comparable in outcome (Baker et al. 1977). Also, in both approaches, disulfiram (Antabuse) appears to be a not infrequently used treatment adjunct. Studies by Charuvastra et al. (1976) and Tong et al. (1980) on the combined use of methadone and disulfiram indicate that the combination appears to be a safe one. One group studied eight patients for up to 16 months with various blood chemistry tests and found no abnormalities. The other found that disulfiram had no effect on opiate intoxication or abstinence symptoms, and although it lowered the plasma methadone level and shortened its terminal halflife, such changes were not statistically significant.

It is, of course, one thing to say the combined use of methadone and disulfiram is safe and another to get patients to use the drug on a regular basis. Pascarelli and Eaton (1973) suggested on the basis of the alcoholism literature that the methadone patients least likely to succeed on disulfiram would be those under 40, with a history of blackouts, currently depressed, and of low social stability. They emphasize that the drug must be used as part of a total treatment program but do not describe such a program. Gerston et al. (1977) list a comprehensive program as "a combination of supportive environments and psychotherapy, crisis intervention, and an emphasis on control of drinking." They also note that whereas one study found success to be correlated with the number of therapeutic modalities available (Kissin 1972), an "exhaustive literature review found that minimal or no treatment at all had the same effect on abstinence as more than minimal treatment" (Emerick 1975).

Liebson et al. (1978) compared 25 alcoholic methadone-maintained patients divided into two groups on a random basis. One group was required to take disulfiram as a condition of getting their methadone while the other was urged to take it but could get their methadone regardless. The first group did substantially better than the second in regard to drinking (2 percent of days with drinking vs 21 percent), and this requirement did not drive the patients away from the methadone program. Because the ethics of denying methadone to patients who refuse disulfiram may be questioned, the authors suggest "this approach be considered only for those patients for whom all else has failed and whose alcoholism has already resulted in a decision to terminate methadone maintenance." Kamback (1979) has tried a similar contingency method of disulfiram administration on 10 methadone patients and also reports good results in terms of alcohol abuse and lifestyle change. He cautions, however, that methadone may ameliorate some of the adverse consequences of the disulfiram-alcohol reaction and, therefore, a daily breathalyzer test should be used to monitor alcohol intake. If the test indicates alcohol in the blood, methadone is denied until the alcohol content returns to zero. This does not totally prevent hidden alcohol use since the breathalyzer only detects alcohol use for a 10-12 hour period. Patients could, therefore, drink right after their methadone dose.

Even though alcohol problems may have preceded entrance onto methadone maintenance for most patients and therefore the modality cannot be "blamed" for it, the consequence of such alcohol abuse can be devastating. Programs are well advised to try and treat it. Disulfiram can be a useful treatment adjunct when combined with counseling. However, many patients are reluctant to take it and a contingency method relating intake of methadone to the disulfiram may be necessary to ensure compliance with such a regime. This can raise ethical questions and should be reserved for patients who would be otherwise discharged from the methadone program. Since the number of patients reported in the literature on this regime is very small and followup data inadequate, final conclusions as to the method's usefulness need to be reserved.

SUMMARY

It has been said that many of the physicians who treat addicts are like the addicts themselves in one respect --

they are looking for a drug to do magical things. This paper has summarized the possibilities of applying such magic, if not significant pharmacologic help, to a variety of psychiatric problems that may accompany narcotic addiction. It has been shown that many of the patients do have such difficulties, with affective disorders being most common. Methadone may have a direct impact on the expression or emergence of a number of psychiatric symptoms, but as yet its role is not clear. As far as the various psychotropic drugs are concerned, neuroleptics for schizophrenics and lithium for manic disorders are generally agreed upon. A more extensive trial of lithium in a variety of situations seems indicated. Minor tranquilizers for anxiety and MAO inhibitors for depression are both seen as problematic in this population -- the former because of the possibility of abuse, the latter because of the danger of drug interaction associated with the addict's careless lifestyle. Tricyclic antidepressants may have a role in treating major depression in methadone-maintained patients, but the liability of the syndrome over time with frequent spontaneous remission argues against their routine use until it is clear the depression has persisted 3-6 months into methadone treatment. Finally, disulfiram may be useful in treating the alcoholic methadone patient, if he will take it; a contingency method using methadone may be necessary to accomplish this.

Concomitant severe psychopathology has been associated with poorer outcome while on methadone. Chemical and psychological approaches that can reduce its severity could significantly improve the quality of patients' lives both during and after methadone maintenance.

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CRITIQUE

Donald F. Klein, M.D.

This review raises the important issue of the utility of psychoactive drugs in the methadone maintained opiate addict with psychopathological manifestations.

The opening sentence reflects the general confusion with regard to the goals of the use of psychoactive pharmacological agents. Are drugs being used to relieve dysphoric affects that are life-situation appropriate, such as everyday anxiety or dysphoric feelings secondary to disappointment? In the more extreme case, are drugs used to alleviate chronic dysphoria secondary to chronic, massive demoralization, which in turn is due to massive life deprivations?

Are drugs used to treat pathophysiological derangements, true disease states which incur maladaptive changes in thinking, feeling, and behavior? Note that these maladaptive changes per se are not necessarily dysphoric, as in the case of mania. Are drugs in themselves sufficient to induce a pathophysiological disorder, which then requires more drug for stabilization, thus inducing a vicious circle? Are drugs used to institute a supernormal state of euphoria, and does this represent a type of recreational self-indulgence?

The problem is that much of the time we simply do not define which goal is being pursued when psychoactive drugs are used.

The issue is not too difficult to resolve when we are talking about medication, such as the antipsychotics, tricyclic antidepressants, and lithium, which clearly do not induce euphoric states in the normal person, nor do they relieve the ordinary dysphorias created by the vicissitudes of daily living. It is noteworthy that none of these agents have any street use or black market associated with them. Therefore, their prescription is narrowly defined as for the treatment of disease.

Those treatment staff members who object to the use of such medication in the treatment of the methadone-maintained patient have a conceptual confusion that requires clarification by medical staff.

The only possible exception to this rule is with regard to the use of amitriptyline, which apparently has, at least in some cities, found a black market, perhaps exclusively among methadone-maintained patients. For them, it apparently has reinforcing effects.

The nature of this effect is quite obscure, although the report by Liu and Wang (1975) that desipramine raises rat brain methadone levels indicates a possible unique utility for tricyclics via this drug interaction in methadone-maintained patients. Yet another reason for the self-prescribed use of amitriptyline in the methadone-maintained patient may be the well known sedative effect of amitriptyline. However, these effects are entirely insufficient to create a black market for people who are not concomitantly on methadone.

Experimental work in humans concerning interactions of tricyclics and methadone is necessary to resolve the issue. The material reviewed by Kleber shows that such studies are few indeed and difficult to interpret.

Tricyclic Antidepressants

Kleber quite properly turns immediately to the issue of diagnosis. Modern pharmacological practice emphasizes that the most discriminating use of medication is obtained by abjuring a target symptom approach and moving to a syndromal or diagnostic approach. For instance, imipramine is useful for the agoraphobic patient, but of no value for the simple phobic.

The fact that Kleber has shown a very high lifetime incidence of depressive disorders in opiate addicts makes the resolution of the question of the utility of antidepressant drugs all the more pressing.

Of interest is the contrast between the study by Woody et al. (1975), which seemed to indicate the utility of doxepin in a double blind placebo controlled study, and Kleber's study. However, it is noteworthy that Woody et al.'s study was during early program adjustment with increasing doses of methadone. Kleber et al. were unable to reproduce Woody et al.'s results. However, here the patients were already in a maintenance phase of the methadone program. They also showed a very high placebo response rate.

Several questions come to mind. Is it possible that in the Woody et al. study the patients were actually suffering from moderate degrees of opiate abstinence during the period of early methadone adjustment and that the putative increase in methadone brain level produced by tricyclics was found rewarding by these patients?

On the other hand, what were the methadone stabilization levels in the Kleber et al. study? Were they sufficiently high so that even moderate increases due to the putative amitriptyline interaction were not found particularly rewarding? Did the Kleber et al. study suffer from a type two error in that, if one has a 60 percent placebo response rate, one needs very large sample sizes to detect real drug effects? Kleber does not specify in this review his sample size or the relevant power analyses.

Yet another question concerns the comparative diagnostic composition of these two studies. Diagnosing depression, although greatly helped by the use of SADS and RDC, is not a simple matter, and it can well be obscured by temporary stress-related affective states. Further, retrospective analysis is always difficult and made all the more difficult if the patient is episodically using various mood-altering agents. In my experience, patients can seldom recall whether a period that, in retrospect, sounds like a clear, major depressive episode occurred in a drug free period.

Kleber concludes that one should not rush in to treat depressive symptoms with tricyclic antidepressants, but they could be considered for those who do not develop a remission over the 3-6 months post-admission.

My own conclusion differs somewhat. It seems to me that there has been insufficient clinical experimentation with tricyclic antidepressants in this patient group. There is a substantial likelihood that at least a subgroup of these patients may benefit from tricyclic antidepressants. How to define this subgroup in terms of clinical symptomatology, past history, family history, etc., is plainly a task for the future. However, it is a task that will not be solved without accumulated clinical experience. Therefore, I would encourage the use of tricyclic antidepressants in methadone-maintained patients who still manifest a depressive reaction after approximately 2 months of stabilized methadone treatment. After sufficient pilot clinical data have been obtained, then proper controlled trials are mandatory.

These recommendations seem congruent with Kleber's discussion of the possible utility of lithium.

The question of panic disorder as an antecedent to opiate addiction and its possible specific treatment with tricyclics needs exploration. It is of interest that Kleber reports a remarkably high incidence of phobic disorders, and such disorders not infrequently conceal a panic disorder (Quitkin et al. 1972).

Lithium

Kleber refers to several papers which report on small numbers of patients treated in an uncontrolled, open fashion. The results are less than clear-cut. If anything, the major arguments in favor of the use of lithium are theoretical rather than clinical.

Kleber concludes, "Wider use of lithium in a few selective methadone programs might be encouraged so as to gain more clinical experience with combining the two modalities and to focus more clearly on the types of patients that may be helped. If clinical experience indicates sufficient usefulness, blind clinical trials can be then undertaken." I agree with this statement, but the logic behind it can be applied with equal force to the tricyclic antidepressants.

MAO Inhibitors

Kleber refers to the possibility that MAO inhibitors may have abuse potential. There is a relative lack of information concerning the effects of MAO inhibitors upon normal people. Several papers suggest that these drugs are not euphoriant in normals but actually produce sedation. The amphetamine-like mood effects that have been noted may actually represent the interaction of MAO inhibitors with the pathophysiology of the atypically depressed patient, rather than being a direct stimulant effect. More extensive trials of MAO inhibitors in normals would be illuminating. Again, there does not seem to be any black market in MAO inhibitors and their abuse potential in opiate addicts is quite unknown.

Kleber seems more concerned, however, about the risks of serious reaction due to a self-exposure to tyramine-containing agents in a drug-abusing population which is notoriously careless with regard to drugs, alcohol, and

food intake. These concerns are clearly realistic. Nonetheless, there is accumulating information that one subgroup of depressives, defined as atypical depressives, may specifically benefit from MAO inhibitors. I have had personal experience with several amphetamine addicts who benefited from MAO inhibitor treatment.

Interesting areas for future exploration exist. One is the utility of drugs such as deprenyl, which are specific MAO-B inhibitors and seem quite safe since they may not have the potential for the cheese reaction. Such drugs might actually be of considerable benefit in treating the postmethadone withdrawal lassitude and apathy often reported by opiate addicts, since their symptomatology closely resembles that of atypical depression.

Yet another, seemingly even more outlandish idea, would be the use of combined MAO inhibitor and tricyclic medication treatment. Strange to say, it is possible that this combination is actually safer than the use of MAO inhibitors alone. The argument is that when administered simultaneously, the tricyclic antidepressants would block the uptake of tyramine, which is an indirect pressor agent. Therefore, the combination might be less likely to produce a paroxysmal hypertensive crisis than the use of MAO inhibitors alone.

Clearly, this is an area that should first be clarified in animals, human volunteers, and ordinary depressive populations before extending the possible benefits of combination antidepressant treatment to patients on methadone maintenance.

Schizophrenic Disorders

Kleber clearly states that the methadone-maintained addict with schizophrenia requires antipsychotic medication. There is nothing to disagree with here. That the drug should be used cautiously because of the possibility of tardive dyskinesia is of course true, but this caution applies to all patients. Kleber suggests that lower doses of antipsychotics than normal might be employed because of a synergistic effect with methadone. This is a researchable question, and one that would in fact have considerable heuristic interest. Unfortunately, because of the low rate of schizophrenia in the methadone-maintained population, it seems unlikely that this study could be carried out except by an extensive collaborative trial.

Alcoholism and Disulfiram

That alcoholism is often associated with methadone maintenance seems indisputable. Whether it reflects an antecedent condition or is actually due to the patients' attempt to circumvent the methadone blockade of opiate euphoria is not clear. However, making this distinction does not seem relevant to the question of whether disulfiram is a practical treatment for such patients. The data provided by Kleber indicate the high likelihood that it is a safe and effective treatment, but there is some question whether it is an acceptable treatment.

The issue is raised as to whether the use of disulfiram may not be made a condition for continued methadone maintenance. Although different ethical stands are possible, I believe that such a contingency management approach is not only ethical, but it might be unethical not to do so, if simpler modes of management are ineffective and the degree of alcoholism is clearly dysfunctional. Kleber suggests that this might be limited to the group of patients whose alcoholism has already resulted in the decision to terminate methadone maintenance. I think my threshold for the use of contingency management programs would be somewhat lower.

Yet another unexplored area is the development of a long-acting disulfiram, which would plainly extend the clinical utility of this agent.

Minor Tranquilizers

This is one of the most difficult areas because of the clear abuse potential of these agents in these patients.

That benzodiazepines are useful in calming anxiety seems indisputable. That many patients maintained on methadone are anxious, or at least claim to be anxious, is also clear.

Plainly, the clinician is in a dilemma. The clinical strategy employed must depend upon a weighing of relative risks and benefits. Does the possible amelioration of anxiety in one subgroup of methadone-maintained patients outweigh the possible induction of benzodiazepine abuse in another subgroup?

My own view may be unduly fatalistic, but it seems to me that if certain patients have a high potential for benzodiazepine abuse, then they also have a high potential for alcohol abuse, and that is available upon every corner. Therefore, the idea that benzodiazepine prescription will induce a whole new form of drug dependence seems unreasonable. That does not mean, of course, that if benzodiazepines are prescribed that they will not be abused, but simply that no new pathological condition is likely to be incurred. Therefore, I would prescribe benzodiazepines as an adjunct to methadone when there is sufficient clinical indication in the form of a generalized anxiety disorder or atypical anxiety disorder.

Kleber's wise clinical recommendations with regard to monitoring the use of benzodiazepines should, of course, be followed, and if the patient develops chronic benzodiazepine intoxication, this clearly requires treatment. However, I do not think that fear of such an untoward outcome should prevent us from the diagnostically indicated prescription of these agents, even recognizing the high probability of abuse.

Whether alternative forms of anxiety reduction, such as relaxation training, might prove equivalently valuable and less dangerous is a researchable question. I became interested in the possibility of a comparative trial of relaxation techniques with benzodiazepines in nonaddicted anxious patients and was amazed to find that not a single appropriately controlled, comparative trial of pharmacological and nonpharmacological methods of anxiety and tension reduction has been carried out. If this has not been done with ordinary psychiatric patients, it is not surprising that it has not been tried with methadone-maintained patients. Nonetheless, perhaps it is precisely in this group of patients where the impetus might be great enough, because of the heightened danger of benzodiazepine abuse, to get trials off the ground.

Kleber is to be complimented on an even-handed, thoughtful, complete review of the available information with regard to the use of psychoactive drugs in the methadone-maintained patient. It seems clear that far too little research has been done. It also seems likely that this may well be due to an ideological set in the mind of many addiction treatment staff who thoughtlessly equate the treatment of illness with avoidance of life responsibilities or the search for the supernormal high. Hopefully, once this ideological confusion is dealt with, clinical

experience with these powerful psychotropic agents can be expanded and may eventuate in properly controlled clinical trials with this high-risk population.

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DISCUSSION SUMMARY

James R. Cooper, M.D., Fred Altman, Ph.D., and Kim Keeley, M.D.

Although there were minor differences between Dr. Kleber's and Dr. Klein's papers on the appropriate clinical indication for the concomitant use of a number of the drugs, the only substantial difference in the recommendations made in the two papers was with respect to the use of benzodiazepines. Because of their abuse potential and actual abuse by methadone maintenance patients, Dr. Kleber cautioned against the use of these drugs in this population, while Dr. Klein suggested that when diagnostically indicated, these drugs were appropriate to use with close medical monitoring despite the potential for abuse.

Everyone agreed that (1) the benzodiazepines are effective anxiolytics; (2) not infrequently, methadone maintenance patients experience generalized anxiety; and (3) the benzodiazepines are abused by this population (according to Dr. Ginzburg, 13 percent of admissions to the Treatment Outcome Prospective Study (TOPS) methadone programs were daily benzodiazepine abusers). The majority of participants were concerned about using benzodiazepines in this population for the reasons indicated. With the exception of Dr. Klein, the participants were reluctant to recommend the use of benzodiazepines as anxiolytics in the population. However, if practitioners do use these drugs, they recommended appropriate diagnostic evaluation, close medical supervision, and use limited to brief periods.

Parenthetically, Dr. Klein noted that some patients with anxiety, insomnia, or panic disorder who are not narcotic dependent seem to benefit from the long-term use of diazepam in small amounts. Instances were described where such patients are "maintained" on 5-10 mg diazepam for years. Hollister's recent paper[1] documenting a benzodiazepine effect after 15 years of usage suggests that a stable, reproducible clinical benefit can be seen with chronic use without the development of tolerance or physical dependence. Such phenomena underscored the biochemical and pharmacologic complexity of drug use and dependence states, regardless of whether the use of benzodiazepines, opiates, or other compounds is being considered.

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[1]Hollister L.E.; Conley F.K.; Britt R.H.; and Shuer, L. Long term use of diazepam. JAMA 246:1568-1570, 1981.

There was general agreement that further research in the entire area of the use of other psychoactive drugs, along with methadone, is needed.

CHAPTER 5. METHADONE DETOXIFICATION FROM ILLICIT OPIATES AND METHADONE MAINTENANCE

Richard Resnick, M.D.

OVERVIEW OF LITERATURE

The primary objective of opioid detoxification treatment is to provide symptomatic relief from the opioid abstinence syndrome while physical dependence on opioids is being eliminated. Because there is cross-tolerance and cross-dependence among all opioid drugs, any one of them could be used to prevent withdrawal symptoms and gradually detoxify the addicted patient.

Methadone is the only opioid drug currently approved for treating opiate dependence and is the detoxification agent routinely employed. The patient is first stabilized on a dose of methadone sufficient to prevent withdrawal symptoms and then detoxified by stepwise reductions in the daily dose. Similarly, for patients attempting to withdraw from a more extended period of maintenance treatment with methadone, stepwise dose reductions are the standard detoxification method. Among methadone-maintained outpatients who attempt to detoxify, the reported incidence of success in achieving a zero methadone dose ranges from 28 percent (Lowinson and Langrod 1974) to 75 percent (Cushman and Dole 1973).

Some clinicians believe that the reason why many apparently rehabilitated patients are unable to achieve abstinence is the symptoms that emerge during or immediately after withdrawal. Efforts to prevent or to minimize these symptoms have focused mainly on varying the rate of methadone dose reductions. For methadone maintenance patients a minimum withdrawal period of 4 to 6 months is often recommended. However, despite individualized and very gradual dose reductions, sometimes extending over several months, most patients experience considerable withdrawal discomfort at methadone doses below 20 mg. Senay et al. (1977) conducted the only experimental study comparing methadone withdrawal rates. Their results show that methadone-maintained patients whose daily methadone dose was decreased by 10 percent per week had more symptoms, higher drop-out rates, and greater illicit narcotic use than patients withdrawn by a 3 percent per week decrement in daily methadone dose.

Other reports indicate a favorable outcome with more rapid withdrawal methods and emphasize the importance of considerations other than rate of withdrawal. For example, Stimmel et al. (1982) suggest that the rate of detoxification may not be a significant factor in determining detoxification success, based on finding no correlation between duration of detoxification and the patient's ability to complete detoxification. Asher (1973) described minimal symptomatology in three addicts who were rapidly withdrawn while in jail, all of whom previously had experienced severe symptoms during attempts at slow withdrawal from methadone in medical settings. Asher also cites a report by Isbell et al. (1948) of mild withdrawal effects after abrupt cessation of methadone doses higher than those currently used in maintenance programs. Blachly et al. (1975) cite evidence that "abrupt withdrawal may be more humane" than a slow schedule, referring to a 1930 report showing less discomfort with abrupt abstinence than with 7- and 14-day withdrawal schedules (Report of the Mayor's Committee 1930). Resnick et al. (1975) withdrew four hospitalized patients from up to 100 mg methadone by dose decrements of 50 percent per day. These patients showed no overt signs of withdrawal and complained only of insomnia and irritability.

Lal and Singh (1976) report on 20 hospitalized opium addicts who were stabilized on 10-30 mg methadone and then randomly assigned to withdraw by one of two methods under blind conditions: 1) gradual reductions of methadone dose over 10 days, or 2) maintenance on methadone dose for 10 days followed by abrupt withdrawal of the methadone completely on day 11. Patients withdrawn by gradual decrements in methadone dose showed a significantly higher incidence of withdrawal symptoms (9 of 10 vs 4 of 10), which were also more severe and longer lasting, compared to patients whose methadone was withdrawn abruptly.

Several investigators have reported on the safety and acceptability of naloxone-precipitated withdrawal as a technique for extremely rapid opioid detoxification (Blachly et al. 1975; Kurland and McCabe 1976; Resnick et al. 1977; Jaffe, personal communication, 1979; Riordan and Kleber 1980). This procedure is particularly useful for patients scheduled for naltrexone treatment, because it shortens the time they are at risk of relapsing before they are "protected" by the antagonist. The popularity of the procedure was due to many patients preferring a brief, albeit more intense, episode of abstinence instead of the milder

but more prolonged episode usually experienced under gradual detoxification procedures. Wen (1977) detoxified 41 out of 50 patients by injections of naloxone using acupuncture with electrical stimulation (AES) to relieve precipitated withdrawal symptoms. No controls were included, but patients claimed that their withdrawal symptoms were better tolerated when AES was given than when the current was decreased or stopped.

The treatment of opioid abstinence by acupuncture has been reviewed by Ng and Wen (1981), who conclude that there is an impressive array of favorable reports on the effectiveness of acupuncture, although none of the studies utilized controls or standardized procedures.

Twenty-one-day outpatient detoxification programs were instituted primarily to serve addicted individuals who were ineligible for methadone maintenance because of their having less than a 2-year history of opioid dependence. Evaluations of the 21-day detoxification programs concur in concluding that they are insufficient to alter addictive behavior and few patients even complete the scheduled withdrawal (Kahn et al. 1976; Campo et al. 1977; Martinez and Cormier 1977; Newman 1979). They appear to be utilized mostly by individuals whose supply of opioids is temporarily unavailable or who are seeking to reduce rather than to eliminate heroin use. Offering an alternative to having to procure and self-administer illegal drugs provides a benefit to society as well as to the clients they serve. Patients may also benefit from these programs by receiving crisis intervention or referral to community agencies that might otherwise be unavailable.

Fulwiler et al. (1979) allowed patients to regulate their own methadone dose during the first 14 days of the 21-day detoxification, which resulted in their receiving higher methadone doses and having fewer heroin positive urines. Tennant, et al. (1975) administered, under double blind conditions, propoxyphene napsylate or methadone to 36 outpatients for 21-day detoxification; the results indicated no significant heroin abstinence in either group and no outcome differences between the two treatments, even though methadone was more effective in suppressing abstinence symptoms.

Tennant et al. (1978) compared, under double blind conditions, detoxification over 42 days by decreasing daily methadone doses supplemented 12 hours later by propoxyphene napsylate (M-PN group), with decreasing daily

methadone doses given in two equal doses 12 hours apart (M-M group). Twenty-two well rehabilitated methadone-maintenance patients served as subjects. All 12 subjects in the M-M group completed detoxification (100 percent), compared with only three of 10 subjects in the M-PN group (30 percent), although the outcome of both groups 1 month post-detoxification was not significantly different.

Many reports on the outcome of patients detoxified from methadone suggest that detoxification success is fostered by providing counseling and other rehabilitation services. This clinical impression has been systematically evaluated in only one experimental study, which showed slightly greater detoxification success rates among patients who were randomly assigned to receive individual psychotherapy compared to patients who received medical and concrete services without psychotherapy (Resnick et al. 1981). Another study of methadone withdrawal techniques suggests a more favorable outcome with a treatment team conducting group therapy for patients detoxifying from methadone, compared to individual therapy, milieu therapy, and nonspecific group therapy (Chappel et al. 1973).

DISCUSSION

There does not appear to be any optimum method of detoxification that is applicable to all patients, nor is it likely that one will be defined among the options now available. Current information suggests that it is most appropriate to individualize detoxification regimens. Decisions concerning the rate of detoxification, the use of methadone or other detoxification methods, and whether detoxification should be done on an inpatient or outpatient basis, whether dosing is blind or open, self-regulated or physician-regulated, cannot be generalized and need to be based on the patient's preference, on a clinical assessment of the patient's needs, and on the experience and resources of the treatment staff. The addition of the alpha-adrenergic drugs to the detoxification armamentarium has been an important recent contribution (Washton and Resnick 1981). The use of clonidine and lofexidine is reviewed elsewhere in this book. The effectiveness of acupuncture and its potential role as a detoxification treatment needs to be delineated through controlled clinical trials.

Whatever detoxification methods are used, the ability of addicted individuals to succeed in withdrawal and to remain abstinent is highly problematic. Followup studies consistently show high rates of relapse to opiate use after detoxification, so higher priority should be given to the study of factors that affect the ability of patients to maintain abstinence than simply to methods of achieving a detoxified state. The withdrawal syndrome is only one of many factors that perpetuate addiction, and its relative importance in recidivism remains questionable. There is not evidence to support the notion that improving detoxification methods above and beyond those already available will increase the number of individuals who are able to achieve an opioid free state.

Factors other than withdrawal symptoms often contribute to detoxification failures (Washton and Resnick 1981). The use of opioids to cope with distressing circumstances and the contribution to relapse of environmental cues and classical conditioning have been extensively discussed in the literature. The patient's "readiness" may be the overriding factor determining whether detoxification from methadone maintenance will be successful. Stimmel et al. (1977) found a high correlation between staff judgments regarding whether or not a patient "completed treatment" with methadone maintenance and the subsequent outcome with detoxification.

Furthermore, detoxification is neither desirable nor appropriate for all opiate addicts, despite the usual expectation that abstinence should be the primary goal. Many addicted individuals obtain beneficial psychotropic effects from opiates and use these agents as self-medication to relieve symptoms of chronic emotional distress. This type of patient will probably do better with long-term methadone or LAAM maintenance, since these medications can enable them to feel and function more normally.

While it is unrealistic to aim for long-term abstinence as an outcome of detoxification treatment alone, when viewed in the context of a multimodality treatment approach, detoxification can be seen to play several important roles. For example, it is the first step toward opiate free functioning and a gateway to other modalities such as drug free and opiate antagonist treatments. For some addicts, the 21-day detoxification treatment represents their initial entry into the treatment system, which may be critical in fostering continued involvement in the rehabilitative process (Newman 1979).

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CRITIQUE

Robert G. Newman, M.D.

Dr. Resnick alludes to some of the published papers describing experiences with various detoxification regimens. He notes the major distinctions which characterize the different methodologies: duration of the detoxification regimen, proportionate dosage decrements, inpatient and outpatient settings, the use of narcotic antagonists to precipitate abrupt withdrawal, and the varying degrees of "supportive services" which are provided along with the medication.

The review is by no means exhaustive; there are innumerable studies which are ignored, though in terms of methodology and number of subjects, they are at least as relevant as the few which are cited. Perhaps constrained by the focus of this chapter, Dr. Resnick does not describe in detail a great many published reports of other detoxification techniques: utilization of nonopiate drugs (e.g., propranolol), narcotics other than methadone (e.g., propoxyphene), herbal mixtures (e.g., that employed in Thailand by Phra Charoon, who received an international prize for the alleged success of his technique), and nonmedicinal approaches (e.g., acupuncture).

I am sympathetic to Dr. Resnick's evident reluctance to cover all the ground which could have been included. The fact is that the bottom line clearly would have remained the same even if his paper had extended to several volumes, with a bibliography of many hundreds of references. The conclusions to be drawn from the literature, whether reviewed selectively or exhaustively, are threefold:

1. Results of programs utilizing what appear to be similar approaches vary markedly, thus creating confusion and skepticism, and precluding generalizations. Dr. Resnick's brief paper refers to these discrepancies in quantitative terms (ability to achieve "zero methadone dosage" among maintenance patients, ranging from 28 percent to 75 percent), and in more general terms (higher drop-outs and more heroin use with more rapid withdrawal in one report, and "favorable outcome" with rapid withdrawal methods in another).

2. There is a seemingly endless variety of approaches and combinations of approaches which can be used to achieve partial or complete "detoxification."

3. Virtually none of the innumerable detoxification regimens described is viewed by the clinician/investigator (and perhaps by the reviewer) as "successful."

None of these three conclusions are surprising:

1. Programs that appear to utilize similar techniques generally differ in many ways: voluntary vs coerced patients; number and background and quality of staff; objectives of staff and patients; characteristics of patients; etc. Equally important, they frequently employ disparate methods of collecting, analyzing, and reporting data which allegedly reflect their experiences.

2. Pharmacological principles that are beyond dispute dictate that gradually diminishing intake of narcotics (<u>any</u> narcotics) will decrease dependence and tolerance levels, which is what detoxification is all about. Indeed, the same result universally follows abrupt cessation of narcotic intake with no "therapy" whatever. Consequently, it is exceedingly difficult to design a "treatment" which does <u>not</u> achieve detoxification.

3. "Success" is precluded not because of any inherent shortcomings of the therapeutic measures applied, but because of the way in which success is defined. The definition of success almost invariably does not stop at <u>achieving</u> abstinence, but demands <u>maintaining</u> that abstinence as well. Contraceptive devices would hardly enjoy much "success" if they were evaluated according to the number of pregnancies occurring after the pill is stopped, or the IUD removed, or the diaphragm no longer inserted.

The fact is that detoxification is one of the easiest, cheapest, safest, and surest medical objectives to achieve, and one that is in tremendous demand by the addict population. Provided one does not continue the

administration of constant (or increasing) doses of a narcotic drug, it is impossible to go wrong. While, as has been stated above, an extraordinary variety of techniques has been proposed, the one which makes the most sense pharmacologically is the administration of a gradually diminishing dose of a narcotic. The oral efficacy and long duration of action of methadone make it the medication of choice for this purpose, not just theoretically, but empirically on the basis of over three decades of use. Just how "gradually" the dose of methadone should be reduced should be determined primarily by the patient's subjective response. To attempt to draw generalizations regarding 21 days, or 3 months, or 12 months, is futile and, I believe, irrelevant from a clinical standpoint, though thanks to the Food and Drug Administration fiat it admittedly is far from irrelevant from a legal standpoint.

So why all the interest in detoxification techniques? Why has there appeared such an incredible collection of papers describing what anyone with a smattering of pharmacological awareness (and certainly every narcotic addict) could predict with confidence? The answers to these questions relate to the third conclusion: the definition of success which almost universally is associated with detoxification. There is consensus (almost) that it must be possible to withdraw the narcotic addict from his or her physical dependence in such a way that abstinence is achieved and then persists, and all we need is the precise technique that can attain this goal. It is a happy thought, a lovely goal to strive for, a Nobel-worthy discovery if ever there was one. But while we think, and hope, and search, and dream of honors bestowed by the King of Sweden, we must acknowledge that in the voluminous literature there is absolutely nothing which supports the notion that such a breakthrough has occurred, nor that it is just around the corner.

And meanwhile? Meanwhile, resources must be applied to maintain on methadone those former heroin addicts who wish to continue receiving such treatment and who, objectively and subjectively, benefit from it. Meanwhile we must examine the characteristics of our methadone maintenance programs and the image they invoke in the community. These factors play an important role in motivating successful patients to wish to abandon effective treatment, even at tremendous risk. Meanwhile, for street addicts who wish to lower their level of narcotic dependence through partial or complete withdrawal, we should be guided by what we know of basic opiate pharmacology, and

not by unfounded medical, social, or political theories. And finally, we must pay more attention to our patients -- their goals, their needs, and their response to the treatment we provide -- and less to rigid protocols which are prompted by governmental fiat and/or by research protocols which promise to tell us little if anything that we do not already know.

DISCUSSION SUMMARY

James R. Cooper, M.D., Fred Altman, Ph.D., and Kim Keeley, M.D.

There was considerable discussion about the objectives for detoxification treatment. The opinion was unanimous that a distinction should be made between success in reaching a zero dose and maintaining abstinence after detoxification, and that the objective for the current procedures should be restricted to reaching zero dose. Dr. Goldstein, as well as others, suggested that changing the name of the current procedures from "detoxification" to "pharmacologic amelioration of withdrawal illness" might help reduce the confusion about the objectives for detoxification treatment.

Although many patients do not successfully complete detoxification or maintain abstinence, there was strong support for providing detoxification (pharmacologic amelioration of withdrawal illness) services for both individuals addicted to street narcotics and individuals in methadone-maintenance treatment. For methadone-maintenance patients there was a consensus that the physician, in conjunction with the patient and other staff, is best able to determine when detoxification is likely to be successful, and consequently the detoxification decision should be made by the physician in conjunction with patient and other staff. There was general agreement with Dr. Resnick's conclusion that there is no optimum detoxification method for all patients. The consensus was also that the detoxification regimen (ranging in duration from several days to 6 months) should be individualized by the physician in conjunction with the patient; thus the current Federal statute and regulation that limits the detoxification process to a maximum of 21 days needs to be modified to reflect the existing state of the art.

For "street" addicts, Dr. Newman expressed the sentiments of the group when he suggested that more detoxification facilities ought to be made available since they provide an immediate source of treatment for those who want to reverse or at least reduce their acute physical dependence on opiates. This is a highly relevant goal from the standpoint of both the patient and the community. Providing such services clearly has an impact on crime, individual health, and, on occasion, introduces the patients to other components of the treatment system.

Various detoxification variables were discussed. The reported acceptability to some patients of abrupt termination or extremely rapid withdrawal from narcotic drugs (1 to 2 days) was noted. Dr. Senay suggested that a 4-6 month detoxification regimen was often preferable to a 21-day or less detoxification regimen. There was some discussion about environmental stimuli associated with drug taking which may contribute to patient failure to reach zero dose or maintain abstinence. The stimuli were thought to produce this effect both directly and through the "conditioned abstinence syndrome" or "pseudo-withdrawal." Beneficial effects of positive reinforcement associated with detoxification were also mentioned. However, there was agreement that regardless of the detoxification regimen used, many patients do not reach zero dose, and the recidivism rate of those who do is very high.

Because of the low percentage of successful outcomes and the variability between studies it was considered impossible to draw conclusions about which treatment variables were related to outcome. No relationship was considered to have been demonstrated between any of the treatment variables reviewed (e.g., rate of detoxification, self-regulation, set, setting) and outcome.

Although the group supported the provision of detoxification services, with the exception of Dr. Kleber, they indicated that further research on detoxification procedures should have a low priority. They believed that the lack of major differences among the various detoxification methods in the percentage of patients reaching zero dose or maintaining abstinence makes it unlikely that detoxification methods could be developed in the near future that would significantly improve the success in either reaching zero dose or maintaining abstinence.

Dr. Kleber favored research to develop methods which would enable a greater percentage of patients to be detoxified from methadone maintenance and to determine whether the percentage of patients remaining opiate free would remain constant when the percentage of patients detoxified is increased by such a method. The second component of the research is necessary because the factors that determine success in reaching zero dose are not necessarily the same factors that determine success in maintaining abstinence. An increase in the percentage of patients reaching zero dose may result in an increase in the percentage remaining abstinent or it may result in an increase in the percentage of patients who relapse.

CHAPTER 6. USE OF CLONIDINE OR LOFEXIDINE TO DETOXIFY FROM METHADONE MAINTENANCE OR OTHER OPIOID DEPENDENCIES

Harold M. Ginzburg, M.D., M.P.H.

INTRODUCTION

The Food and Drug Administration (FDA) has approved the New Drug Application (NDA) for clonidine as a medication useful in the treatment of hypertension. It is an alpha-adrenergic agonist whose mechanism of action in the treatment of hypertension appears to relate to its ability to decrease the sympathetic outflow from the brain in the lower brain stem regions, possibly in the nucleus tractus solitarius (Haeusler 1974). Both efferent parts of the autonomic nervous system have been revealed to mediate sympathoinhibition and vagal activation (Lowenstein 1980; Kobinger 1978). Clonidine activates the post-synaptic alpha-adrenergic receptors in the cardiovascular control center of the medulla oblongata (Schmitt and Schmitt 1969).

In the past 5 years a number of clinical investigators have obtained Investigational New Drug (IND) exemptions from FDA for the use of clonidine as an adjunctive treatment in the detoxification of opioid abusers. A significant amount of administrative and scientific confusion has resulted from the failure of nonscientist and nonresearcher clinicians to appreciate that, though clonidine is an NDA-approved drug, it has not been approved for use in the treatment of conditions other than those indicated in the package insert.

This discussion of clonidine's apparent usefulness in the detoxification of opioid abusers must commence with a review of the acceptable procedures in using this drug (and other drugs in a similar legal status) in clinical research and clinical practice. Any drug which has an approved NDA may be prescribed by a licensed physician in the manner indicated and for the conditions noted in the package insert. If the physician wishes to accept liability for any untoward effects, he may administer an NDA-approved drug in a nonapproved manner. He accepts any additional liability whenever he uses the drug for a condition not mentioned in the package insert or administers

the drug beyond the therapeutic range specified (or in a manner not indicated) in the package insert. It is assumed that the physician, under such circumstances, would discuss the additional risks of the drug with his patient and would obtain a specific informed consent document indicating what information has been presented to the patient and giving the patient's approval for administration of the drug.

If research is being conducted, then approval of the research protocol (including a detailed informed consent form) by the appropriate Institutional Review Board (IRB) is required, as is the filing of the appropriate FDA forms for the IND exemption. Failure to file the IND may leave both the investigator and his parent institution liable for damages should there be any untoward effects in the research subjects. In addition, FDA regulations will have been violated if the drug has been shipped across State lines for use in an unapproved manner. FDA becomes involved only when interstate commerce is involved. Local purchase, and local use for an unapproved purpose, are State rather than Federal concerns.

It appears that a number of clinicians, in both private and clinical practice, have accepted investigators' recommended procedures for using clonidine in the detoxification of opioid abusers without having obtained the informed consent of the patient and, where appropriate, an IND exemption. These clinicians may not appreciate that they are at added legal risk when they use an approved drug for a nonapproved purpose.

PHARMACOLOGIC BACKGROUND

Clonidine hydrochloride (2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride) is an alpha-2 adrenergic blocking agent (Nickerson and Ruedy 1975). The initial pressor response to this drug is due to the direct stimulation of the alpha-adrenergic receptors. The subsequent significant alpha-adrenergic blockade permits clonidine to be classified as a partial agonist. The pressor response, however, is potentiated and prolonged by ganglionic blocking agents which interfere with reflex blood pressure adjustments. Clonidine causes an acute increase in cerebral vascular resistance and a decrease in cerebral blood flow in man (James et al. 1970). Changes in cerebral vascular blood can be anticipated to have a significant impact on blood pressure and central nervous system processes.

Clonidine inhibits the release of norephinephine and cardiac responses to postganglionic adrenergic nerve stimulation (Werner et al. 1972) and is able to produce direct peripheral vasodilatation as well (Shaw et al. 1971). These peripheral effects are insufficient to account for the acute hypotension and bradycardia produced, both of which can be specifically blocked by an alpha-adrenergic blocking agent.

Laverty and Taylor (1969) report that clonidine and chlorpromazine have similar central nervous system effects: marked sedation, a decrease in spontaneous motor activity, conditioned avoidance behavior in animals, and a lowering of core body temperature. However, clonidine does not appear to have any antipsychotic properties. Chronic administration of clonidine has been associated with an increase in irritability and spontaneous aggression (Katic et al. 1972).

Blaschke and Melmon (1980) indicate that almost all of the available pharmacokinetic data for clonidine have been obtained from normal volunteers given single doses of the drug; in the five normal individuals studied, the bioavailability of clonidine averaged approximately 75 percent. Davies et al. (1977) calculated that the elimination halflife averages 8.5 hours. Dollery et al. (1976) found that the hypotensive effect was dose dependent in the 100-μg to 300-μg range; the duration of action, after a single oral dose administered to normal healthy volunteers, was approximately 8 hours. Pettinger (1975) found a greater range in the duration of the hypotensive effect, 4 hours to more than 24 hours, after a single oral administration to patients with hypertension. Wing et al. (1977) compared the effects in normotensive volunteers and patients with essential hypertension and found no qualitative differences in cardiovascular effects, although the action was quantitatively greater in the hypertensive patients.

Clonidine has been marketed in the United States since 1974 by Boehringer Ingelheim, Ltd., in 100-μg and 200-μg tablets and an injectable preparation of 150 μg/ml. Its relatively short halflife precludes a single daily dose for the control of hypertension. At least two unequal divided doses (the larger dose at bedtime) are recommended to minimize the unwanted side effect of sedation. It is not unusual for three to four doses per day to be required for clonidine to maintain its antihypertensive effect. The usual antihypertensive total daily dose is from 400 μg

to 2.0 mg. The average total daily dose used in detoxifying opioid-dependent individuals is approximately 17 μg/kg/day or 1.35 mg/day for the average-sized man and 1.0 mg/day for the average-sized woman, in divided doses taken every 4-6 hours.

The most frequent side effects reported are dry mouth and sedation. Both are common and may be severe. Impotence and constipation are reported in 10 to 20 percent of chronic therapy cases. Allergic responses, including rashes, pruritus, and angioneurotic edema, have also been observed. Hyperirritability and a marked rebound in blood pressure frequently occur when medication is abruptly discontinued. This is associated with a considerable increase in catecholamine excretion and can be controlled by alpha- and beta-adrenergic blocking agents (Hansson et al. 1973). Concurrent administration of tricyclic antidepressant medications can essentially block the antihypertensive effect of clonidine (Briant et al. 1973).

Tolazoline, an alpha-adrenergic blocking drug, can be used to reverse clonidine toxicity or accidental or deliberate overdose because it can penetrate the blood/brain barrier and thereby reverse part of clonidine's central nervous system effects (Pettinger 1975).

CLINICAL APPLICATIONS IN THE TREATMENT OF OPIOID-DEPENDENT INDIVIDUALS

Clonidine has recently gained prominence as a chemotherapeutic agent for the detoxification of individuals dependent upon heroin or other opioids, including methadone. The precise pharmacological mechanisms and sites of action for its use in the detoxification of opioid addicts have not been clearly defined. However, the experiences of Gold, Kleber, Resnick, Washton, and other research groups reviewed below have demonstrated its relative efficacy in decreasing the signs and symptoms of the opioid withdrawal syndrome. At the present time there are more than 80,000 individuals receiving methadone maintenance treatment. In addition, at any point in time approximately 8,000 individuals are in a methadone detoxification program. By FDA regulation, such programs may not utilize a detoxification protocol that exceeds 21 days. FDA regulations do not specify a minimum period for detoxification, nor do they specify a particular decreasing dose pattern. There is no standard protocol for detoxifying patients.

Although Senay et al. (1977) have found that short-term detoxification may not be the most satisfactory means of alleviating the signs and symptoms of withdrawal, there is no specified length of time for methadone detoxification following methadone maintenance. Prolonged detoxification is considered a natural sequela to methadone maintenance treatment. No minimum length of time on methadone maintenance is specified before prolonged methadone detoxification can occur.

Clients allege that they return to street opioids to gain relief from the prescribed detoxification regimens. Detoxification from methadone appears to require a longer period of time and more clinical sophistication than detoxification from heroin. If the average time in treatment in a methadone maintenance treatment program is less than 6 months, according to the National Institute on Drug Abuse (1980) Client Oriented Data Acquisition Process (CODAP) survey of all Federally supported drug abuse treatment programs, and considering that the treatment programs are currently reporting operation at or near 100 percent capacity, then over 160,000 opioid abusers are exposed to methadone maintenance treatment each year. Approximately half of these clients are found to terminate their use of this synthetic narcotic in a nontherapeutic and precipitous manner. Any technique or method involving chemotherapy or other alternative means that is capable of alleviating the signs and symptoms of withdrawal and of preventing or delaying the client's return to illicit opioids or methadone maintenance requires careful consideration and assessment.

Although extensive clinical experience with the use of clonidine in the treatment of hypertension has been accumulated, the effects of the chronic administration of this drug are not well studied (Blaschke and Melmon 1980). Even more important than the lack of knowledge concerning the long-term effects of this drug in treating hypertension is the lack of general knowledge concerning the short, intermediate, or long-term effects in treating opioid withdrawal. Unlike new drugs that require a clinical investigator to file an IND exemption with the FDA prior to obtaining and administering the drug under controlled conditions, clonidine appears to be used in opioid detoxification by many clinicians in an indiscriminate manner. Since at least April 1980, Boehringer Ingelheim, Ltd., has had an investigational brochure available for clinicians who wish to use clonidine hydrochloride in

opiate withdrawal. Only a limited number of investigators are following their protocol (Boehringer Ingelheim, Ltd., personal communication, October 26, 1981).

Tseung et al. (1975) were the first to report, on an animal model, that clonidine inhibited total body shakes and potentiated escape attempts induced by administering naloxone to morphine dependent rats. Fielding et al. (1978) demonstrated, also in animal models, that clonidine possessed dose-dependent analgesic and antiwithdrawal activity, using suppression of morphine withdrawal body shakes as the measure. In addition, he demonstrated that naloxone failed to antagonize the analgesic actions of clonidine but effectively antagonized those of morphine. Thus, in laboratory tests, clonidine appears to be an effective analgesic that antagonizes the signs of morphine withdrawal.

Redmond et al. (1977) and Gold and Redmond (1977) have reported that electrical or pharmacologic activation of the locus ceruleus in nonopioid primates produced behavioral changes analogous to those demonstrated in opioid withdrawal. Morphine and clonidine are reported to have blocked this activation.

Clonidine's role in detoxification or alleviation of signs and symptoms of opioid withdrawal in humans is an extremely recent one. Gold et al. (1978b) reported that a single dose of clonidine relieved the signs and symptoms of opiate withdrawal and that addicts could be successfully detoxified with clonidine under the close supervision of an inpatient hospital setting. A single dose of μg/kg was noted to produce a rapid and significant decrease in withdrawal symptoms, subjective distress, and blood pressure in 11 hospitalized addicts. These addicts had undergone an abrupt discontinuation of their 5-50 mg chronic maintenance dose of oral methadone. Gold and Kleber's (1979) rationale for testing clonidine's efficacy in opioid withdrawal was based on animal studies demonstrating that the increased brain noradrenergic activity associated with opioid withdrawal was markedly reduced by clonidine.

The usual conversion scheme for opioids is that 1 mg of methadone can be substituted for 4 mg of morphine, 2 mg of heroin, or 20 mg of meperidine. Regardless of which opioids are being consumed, the characteristic opioid withdrawal syndrome remains relatively constant. This clinical syndrome may include the following signs and

symptoms: anorexia, anxiety, marked chilliness, coryza, diarrhea, gooseflesh, intestinal spasm, increase in heart rate and blood pressure, insomnia, irritability, lacrimation, nausea and vomiting, myalgias, restlessness, rhinorrhea, stomach and muscle cramps, severe sneezing, violent yawning, and overall fatigue and weakness. The severity of the signs and symptoms is a direct function of the opioid(s) used, their route of administration, their half-lives, and other concurrent drug use, as well as the physical and psychological state of the addict.

SINGLE DOSE TRIALS

Gold et al. (1979b) reported administering 5 μg/kg oral clonidine to six male opiate addicts 36 hours after the abrupt withdrawal of their 15-50 mg chronic methadone dose and to six male heroin addicts who exhibited signs and symptoms of opioid withdrawal. At a 2-hour interval (11 a.m. and 1 p.m.) the subjects received placebo or 5 μg/kg in matched oral vehicles. All trials were double blind. Withdrawal signs and symptoms increased during the 3-hour baseline period (8 a.m. to 11 a.m.). Anxious, tense, and nervous feelings were reported to be relieved by clonidine. There were no reports of clonidine producing a euphoria. Five of the six methadone subjects and all of the heroin subjects were offered oral clonidine in an outpatient trial of 5 μg/kg twice daily for 7 days. The only consistent complaint among all the subjects was occasional sluggishness and a disturbance of sleep continuity. Two-week posttreatment data indicated that all 11 patients were doing well. Blood pressures either after the initial dose or during the outpatient experiences were not presented.

Gold et al. (1978b), in a double blind placebo-controlled inpatient experiment, administered a single oral dose of 5 μg/kg of clonidine to 11 hospitalized methadone dependent volunteers (15-50 mg daily dose) who had been without opioids for the previous 36 hours. Baseline and postexperimental physical and psychological status were established using a sign and symptom checklist. The ratings seemed to indicate that there was a significant differential pattern between the clonidine and the placebo. Within 2 hours after the oral administration, the clonidine patients consistently reported a significant decrease in the symptoms, especially the self-rated "nervousness" and "irritability" items. Blood pressure decreased an average of 18 mm Hg diastolic and an average of 16 mm Hg systolic (from an average of 124/85 to 106/69) per subject.

Ten subjects agreed to receive clonidine as outpatients. The dose was 5 μg/kg twice a day for 7 days. During the 6 weeks (or more) post study, four patients had returned to the methadone maintenance treatment program, though on reduced methadone doses; one patient required tricyclic antidepressants for panic reactions, though he was able to remain opioid free; and seven patients were using no opiates. It should be noted that two of the patients who returned to methadone reported that their failure to remain drug free was the direct result of the help the methadone maintenance clinic provided them in thinking of themselves as "without the ability to get high." The two other patients are reported as having developed major depressive episodes requiring acute psychiatric intervention, one being psychotic and agitated and the other apparently suicidal. Both of these patients are reported as having prior psychiatric hospitalizations for depression. The depressive episodes are reported to have been aborted by the reintroduction of low doses of methadone. Thus, three of the 10 patients being given clonidine in an outpatient clinical trial had severe and disabling psychiatric illnesses apparently precipitated by the clonidine detoxification.

Washton et al. (1980a) presented preliminary data in their attempt to replicate the single-dose findings of Gold et al. (1978b; 1979b). They administered a single oral dose of 5 μg/kg of clonidine to 12 outpatients experiencing acute withdrawal from heroin and methadone. Baseline and postexperimental drug conditions were established using a sign and symptom checklist. Blood pressures were also monitored. All patients reported dramatic relief of withdrawal distress. Chills, lacrimation, muscle and joint aches, perspiration, rhinorrhea, and stomach cramps were reported to be significantly reduced. Lesser, though significant, reductions in anxiety and restlessness (irritability) were also noted. No euphoria was reported. An average decrease of 10-15 mm Hg in both systolic and diastolic pressure was recorded. Other unwanted side effects included dry mouth and drowsiness.

INPATIENT DETOXIFICATION TRIALS

Gold et al. (1979a) reported on 25 patients addicted to methadone, heroin, or synthetic opiates who were treated with oral clonidine subsequent to their abrupt termination from the opioids. Within 90 days of the abrupt termination of methadone, four of the patients had significant

depressive episodes (one became overtly psychotic) and two additional patients had severe panic and anxiety attacks. Thus, six patients had acute psychiatric disturbances apparently precipitated by clonidine detoxification. This is not to suggest that clonidine precipitated psychiatric illness in one quarter of the patients, but rather to indicate that addict patients may have a high concurrent prevalence of underlying severe psychiatric disorders which become clinically obvious when their opioids are withheld. As Kleber and Gold (1978) have noted, though some methadone maintenance patients are in treatment for the opioid addictions, they are also utilizing their methadone as psychotropic medication for their underlying depressive, psychotic, or panic states.

Gold et al. (1978a) conducted an inpatient opioid detoxification study using oral clonidine on 10 previously methadone maintained volunteers (15-50 mg daily dose). All of the patients were screened to determine that they did not have a previous history of cardiac arrhythmia, hypotension, vasomotor instability, psychiatric illness, or hospitalization. The latter two exclusions were included after Gold et al.'s previous experience in precipitating severe psychopathology. However, neither the screening techniques, nor the types and numbers of patients who were rejected from participating in the study, nor those who might have had trouble with clonidine detoxification and its sequelae have been described in the literature.

Gold et al. (1978a) administered clonidine in daily divided doses for 13 days after the abrupt termination of methadone. The total daily dose averaged 17 μg/kg/day for the first 10 days, with a 50 percent dose decrement on each of the next 3 days. No clonidine was administered on the 14th and last day. Oversedation and hypotension were compensated for by lowering the clonidine dose and maintaining the volunteer subject at bed rest. The average decreases in blood pressure were 24 mm Hg systolic and 21 mm Hg diastolic. These changes were noted at 120 minutes and continued during the next 240 minutes (6 hours). In two patients diastolic pressure was reduced to less than 60 mm Hg at 180 minutes after clonidine administration and persisted for another 120 minutes. Six patients complained of difficulty falling asleep. Upon termination of the inpatient clinical trial, 14 days after the last clonidine dose, all 10 patients were opioid free. None of the patients was placed on naltrexone. Eight weeks after the discontinuation of clonidine, half of the patients had used opioids: three patients had episodically used

opiates, one was addicted to a synthetic opiate, and one was readmitted to a methadone program. Despite the initial psychiatric screening examination, one patient required treatment with lithium carbonate subsequent to an acute manic episode. Six months after the clinical trial, one patient was reported as being addicted to dilaudid, three patients were attending a methadone maintenance treatment program, and one was in jail on a drug-related breaking and entering charge. Despite comments by the authors that clonidine could be linked with subsequent naltrexone treatment, this was not attempted with these patients; no explanation is given.

Gold et al. (1978a) noted an important sequel to his and similar research activities: a black market now exists for clonidine. Methadone maintenance clients on doses of 50-100 mg are attempting to self-medicate and self-detoxify themselves to lower doses or abstinence. This could be a dangerous and potentially catastrophic procedure.

Gold et al. (1979c) reported on the inpatient administration of clonidine to 100 volunteer subjects who had been enrolled in a methadone maintenance treatment program immediately prior to their participation in the study. All had requested detoxification from methadone. All were notified that they would have a 36-hour abstinence period prior to the oral administration of clonidine. A sign and symptom checklist, and a vital signs form (including temperature, pulse, blood pressure, and respiration) were completed by a nurse observer. After an initial 6 μg/kg dose of clonidine or placebo, patients without precipitous blood pressure declines were given clonidine 17 μg/kg/day in divided doses for at least 9 days. No reference is made as to whether those subjects receiving an initial placebo subsequently received a test dose to determine whether a precipitous drop in blood pressure would occur when clonidine was administered. No indication is given as to the number of patients who had a precipitous drop in blood pressure nor, if it occurred, how it was clinically managed. There is no indication of of the patient's position (upright, sitting, or supine) when the blood pressures were obtained.

The screening history and examination excluded all patients with a history of cardiac arrhythmias, hypotension, vasomotor instability, and, in particular, a prior history of psychiatric illness or hospitalization. How many patients were screened? And what were the medical and psychiatric diagnoses of those rejected from the study? If

one assumes that the volunteers were typical of those enrolled in methadone maintenance treatment programs, and therefore potentially eligible for clonidine detoxification, then some appreciation of the potential problems would be useful.

The acute first-dose study involved the administration of 6 μg/kg oral clonidine. The results indicated that systolic and diastolic blood pressure were significantly reduced at 120 minutes. Whether or not the individuals were able to function in an ambulatory state is not mentioned, nor is the absolute degree of blood pressure reduction presented. Gold et al. noted that the apparent alleviation of the patients' withdrawal symptoms after 2 hours was independent of whether they had been on low or moderate doses of methadone.

On the first day, the subjects received the initial 6 μg/kg as the test dose (results described above) and then an additional 6 μg/kg dose at bedtime. Commencing the second day of the study, 17 μg/kg were given in the divided doses of 7 μg/kg at 8 a.m., 3 μg/kg at 4 p.m., and 7 μg/kg at 11 p.m. Clonidine doses are reported to have been withheld in some cases owing to severe hypotension, but these cases are not discussed, nor are their numbers recorded. Clonidine doses are reported to have been decreased for excessive somnolence. But again these cases are not discussed, nor their numbers recorded. Additional clonidine was reported to have been given, if needed, but the criteria for this determination are not presented. The majority of the patients (numbers not presented) complained of difficulty falling asleep. No mention is made of the use of sedatives or hypnotics. No rationale is given for the manner in which the clonidine dosage schedule was selected.

Gold et al. (1979c) reported that the affect-related symptoms associated with withdrawal (such as anxiety, irritability, and anger) were rapidly and significantly reduced after clonidine administration. What are the clinical implications of this finding?

Gold et al. (1979c) presented the following advantages of clonidine detoxification:

1. It is rapid.

2. It is a nonopiate.

3. It is noneuphoria-producing.

4. There is a high success of inpatient detoxification.

5. There is a high success of naltrexone induction.

6. It provides drug free or naltrexone alternatives to methadone maintenance for:

   a. pill, cough medicine, or "nonstreet" opiate addictions; and

   b. suburban addicts with no previous exposure to clinic-related drug abuse and crime.

7. It is ideally suited for the working addict.

8. It enhances the role of M.D.s and the M.D.-patient relationship.

9. It defines and limits the role of methadone maintenance.

Items 1, 2, and 3 require no comment. Gold et al. do not describe their criteria of success. If merely completing the protocol is "success," then Gold et al. may have achieved that in all their subjects. Gold et al. do not indicate how well their subjects tolerated the detoxification regimen. No indication is given as to how long these subjects were able to continue to be drug free. No indication is given as to the numbers of subjects inducted on naltrexone or if these subjects remained on naltrexone as long as those inducted on naltrexone, without an initial clonidine detoxification experience.

No evidence is presented of how this proposed treatment regimen will be of assistance to the working addict. Is the addict to be maintained on clonidine? In what manner will the patient-physician relationship be enhanced through the use of clonidine detoxification procedures?

In summary, this paper has a number of significant defects. Gold et al. state conclusions and make observations without presenting the data upon which they are based.

Washton et al. (1980a) presented a preliminary study in an attempt to assess the efficacy of daily clonidine in outpatient detoxification from methadone maintenance. The

outpatient detoxification study had two separate methodologies. Seventeen patients received adjunctive clonidine while their methadone dose (10-50 mg/day) was being decreased at a rate of 5 or 10 mg per week. The remaining 16 patients were switched abruptly from methadone (5-40 mg/day) to clonidine by substituting placebo for active methadone on the day that clonidine was introduced. All patients were given 5 μg/kg/day in divided doses, the dosage then increased by 0.1 mg steps, as needed, to a maximum of .010 mg/kg/day. Outpatient clinic visits were at a minimum of three times a week for clinical evaluation of withdrawal, blood pressure, and adjustment of medication. Ten days after the last methadone dose, an intravenous naloxone challenge dose of 1.2 mg was administered to confirm an opioid free state. This was immediately prior to the subject's being inducted on naltrexone.

Fourteen of the 16 patients (88 percent) who were abruptly switched from methadone to clonidine completed detoxification and were inducted on naltrexone. Only six of the 17 patients (35 percent) who received adjunctive clonidine were eventually inducted on naltrexone. Discontinuing daily clonidine administration after 2-6 weeks apparently produced no ill effects in most subjects. Specific data were not presented. This may have had a subsequent impact on the patient's lack of motivation to be inducted on naltrexone. Six patients in this group (35 percent) did report symptoms; two reported headaches and four reported a partial return of withdrawal symptoms, including nervousness, chills, sweating, and muscle aches. Significant relief of these symptoms followed the resumption of clonidine treatment, a finding that suggests a reaction to abrupt cessation of clonidine may be expected in a significant number of patients receiving the drug for more than a short period of time. Blood pressure data, by study population, were not presented. Neither was the number of instances in which medication had to be temporarily stopped or decreased because of hypotension.

Washton et al. suggested that abruptly switching from methadone to clonidine seemed to suppress symptoms more effectively than adjunctive clonidine administered during gradual methadone detoxification. They indicate that tolerance may develop to clonidine's antiwithdrawal effects after 3 to 4 weeks of daily use. There are at least five alternative explanations or questions which must be resolved before Washton's hypothesis can be accepted. These include the following:

(1) There are different time intervals under consideration. The time for the entire procedure is shorter, with less likely interference from outside conditions in the direct crossover method.

(2) Simultaneous methadone and clonidine administration may result in competitive inhibition of the effects of the clonidine, rather than the development of tolerance to the clonidine.

(3) What were the motivations for the subjects in each group? Did they tire of being subjects?

(4) What was the incidence of hypotension, medication adjustment, and other side effects in the two groups?

(5) What was the incidence and prevalence of psychiatric illness in this population prior to, during, and subsequent to the clonidine phase of the study?

Washton et al. (1979) began the presentation of an expanded study population by restating the single-dose trial results discussed above (Washton et al. 1980a). In this work, an outpatient detoxification study involving a total of 70 patients was presented; 20 received adjunctive clonidine while their methadone maintenance dose was being decreased, and 50 were abruptly switched to clonidine. Twenty-two of this group of 50 patients were on methadone maintenance (5-40 mg/day); the remaining 28 patients were "street addicts" using illicit methadone or heroin. No indication is given as to whether the previously reported subjects are also included in this report.

The detoxification procedure involved induction onto clonidine followed by gradual decrements in methadone at a rate of 5 or 10 mg per week with continued daily administration of clonidine. The rate of clonidine dosage increments was reported to have been tailored for each patient so as to "maximize therapeutic benefit and minimize the occurrence of adverse side effects such as sedation and orthostatic hypotension." No indication of how these decisions were made was presented. Blood pressure, adverse reactions, and other relevant clinical data were not presented, though the authors indicated that the data were

collected. In this study the maximum daily dose of clonidine ranged from 0.2 to 0.9 mg with a mean of 0.8 mg/day, once again indicating the need for careful patient titration.

Time on clonidine plus methadone ranged from 2-6 weeks. Patients who reached a zero methadone dose and remained opiate free for 10 days were given an intravenous naloxone dose, in preparation for naltrexone induction. Clonidine was discontinued at varying rates after the first dose of naltrexone. This would seem to indicate that the patients actually were on clonidine from slightly more than 3 weeks to slightly more than 7 weeks. The potential for rebound hypertension and other complications is not discussed.

Half (10/20) of these patients were not maintained on naltrexone. No indication is given as to how many days beyond the initial naltrexone dose these patients remained on either clonidine or naltrexone. The authors did indicate that abrupt discontinuation of clonidine after 2-6 weeks (as noted above, probably longer) and at least 2 days on naltrexone produced complaints of headaches as well as the more classic withdrawal symptoms, possibly suggesting a competitive inhibition of naltrexone and clonidine. In some subjects, blood pressure values temporarily increased above preclonidine levels, but there was no reported evidence of a clinically significant rebound hypertension. No absolute or statistical data are presented to determine the extent of these effects. The authors concluded that the least problematic method of decreasing clonidine after prolonged use consisted of 0.1 to 0.2 mg decrements per day, until a zero dose is reached. This apparently resulted in no headaches, reemergence of withdrawal symptoms, or abnormally elevated blood pressure values. No data are presented to substantiate these statements.

The rapid detoxification procedure involved both subjects stabilized on a range of methadone doses (5-40 mg/day, mean 19 mg/day) and street heroin addicts. Street addicts using illicit methadone were stabilized on methadone (5-30 mg/day, mean 19 mg/day) for approximately 2 weeks prior to starting detoxification. Those subjects using only street heroin were switched directly to clonidine without interim stabilization on methadone. In this group the maximum daily dose of clonidine ranged from 0.2 to 0.9 mg, with a mean of 0.5 mg/day. This mean is approximately 60 percent

of the dose required by the gradual detoxification subjects (0.8 mg), a fact that suggests a possible interference, or competition, between the methadone and the clonidine for the appropriate receptor sites. This also emphasizes the need for individual patient titration.

Seventy percent of the rapid detoxification group completed the detoxification, had a naloxone challenge, and at least a single dose of naltrexone. No additional information is provided as to the acceptance of and retention on naltrexone. Patients on either methadone maintenance or illicit street methadone were more likely to complete the detoxification regimen and be inducted on naltrexone. Heroin addicts with more expensive street habits were less likely to complete the detoxification regimen than either heroin addicts with less expensive habits or those previously using methadone.

None of the 70 patients reported that clonidine produced euphoria.

Overall, blood pressures decreased 15 mm Hg systolic and 12 mm Hg diastolic (120/80 to 105/68) at the average maximum daily dose of 0.7 mg clonidine. Only six patients reported symptoms of orthostatic hypotension, such as dizziness or lightheadedness upon standing.

Washton et al. (1980b) indicated that the use of large doses of clonidine in the inpatient detoxification of opioid addicts may not be cost effective and, in the long term, may be impractical. Data are presented on 88 opiate addicts who were administered oral clonidine in an outpatient setting after the abrupt termination of chronic methadone maintenance or heroin use. All patients were screened for serious medical or psychiatric illness. Forty-three patients had been on chronic methadone maintenance (5-40 mg/day, mean dose 15 mg/day) for at least 6 months. The remaining 45 patients were using illicit methadone and/or heroin and were not enrolled in a methadone maintenance treatment program immediately prior to their participation in the study. On day 1, all patients were put on placebo methadone and told to take one 0.1-mg clonidine tablet every 4-6 hours as needed for withdrawal discomfort. The total daily clonidine dose was then increased by 0.1 or 0.2 mg on each succeeding day, to a maximum of 1.2 mg, according to each patient's blood pressure and symptoms, in an attempt to reduce withdrawal discomfort without generating side effects such as oversedation

and orthostatic hypotension. The maximum daily dose averaged 0.8 mg (range 0.3-1.2 mg). Twenty-nine of the 43 patients (72 percent) who had been on chronic methadone maintenance treatment were able to remain opiate free on clonidine for the 10 days necessary to initiate opiate antagonist treatment with naltrexone. Illicit opiate users had a 53 percent detoxification completion and naltrexone induction rate. Patients using large amounts of heroin and those on more than 25 mg methadone experienced the greatest difficulty in completing detoxification. All patients reported that clonidine decreased, but did not eliminate, all withdrawal symptoms. Most patients reported having at least one transitory episode of mild dizziness or lightheadedness upon standing. Six patients reported unacceptable dizziness and/or oversedation at clonidine doses as low as 0.3 mg/day. Rapid decrements in the daily clonidine dose at the end of the study led to complaints of headaches and a reemergence of withdrawal symptoms. Reducing the dose by 0.1 or 0.2 mg/day avoided these ill effects.

The authors did not indicate whether any of these subjects have appeared in previous reports. They did indicate that clonidine detoxification is a complex, individual process which requires careful monitoring of the patient by skilled clinicians who understand the nuances of clonidine.

This study, like the others reviewed, demonstrates the narrow therapeutic range of clonidine when it is used to detoxify opioid addicts.

Washton and Resnick (1981) conducted a randomized double blind placebo controlled study comparing clonidine and methadone detoxification procedures. Twenty-six opiate dependent outpatient volunteers who had no recognized serious medical or psychiatric illness were the subjects. Four were women. Nineteen had been enrolled in a methadone maintenance treatment program for at least 6 months, seven were using illicit opioids (heroin and/or methadone) and were not enrolled in a treatment program immediately prior to their participation in the study. This latter group was stablized on a daily methadone dose of 15-30 mg for at least 3 weeks before entering the study. The clonidine detoxification procedure consisted of the abrupt discontinuation of active methadone and simultaneous introduction of active clonidine. The methadone detoxification procedure consisted of methadone dose reductions of 1 mg/day until a zero dose was reached, with simultaneous

administration of placebo clonidine. Most patients received nighttime sedative medication to alleviate insomnia. Neither the number of such patients, the sedative, nor the dose is stated.

Detoxification success was operationally defined by the authors as completion of a 10-day opiate free period following discontinuation of active methadone. Overall, 38 percent (10 patients) successfully completed detoxification. There was no significant difference between the clonidine and the methadone group (4/13 or 31 percent and 6/13 or 46 percent, respectively). Two of the four clonidine patients who achieved the opiate free criterion by day 10 subsequently relapsed to opiate use before completion of the double blind procedure on day 30. Eleven of the 13 methadone patients reached a zero methadone dose. Five of the 11 subsequently relapsed to opiate use during the final 10-day post-methadone period. More than half of the methadone patients either did not complete the study or were not able to remain opioid free for more than 10 days after clonidine detoxification.

Though the major withdrawal complaints were the same for both groups, the clonidine group members reported sedation, dry mouth, and occasional transitory episodes of lightheadedness or dizziness upon standing. They also reported the reemergence of withdrawal symptoms within the first 2-3 days of the study. Patients in the methadone group reported their symptoms much later in the study, when their methadone doses were approaching zero. Washton and Resnick's conclusion was that clonidine detoxification may not be superior to methadone detoxification. An intriguing issue not addressed by any of the current researchers is whether or not underlying psychopathology or personality traits may assist in predicting which type of detoxification may be more appropriate and more successful for a given patient.

Integration of clonidine detoxification into the therapeutic transfer of patients from methadone to naltrexone appears not always to be successful. In this report, however, the researchers may have done themselves a disservice, as they added seven new patients to a larger number of patients who had been enrolled in a methadone maintenance treatment program for at least 6 months. Successful clonidine detoxification and transfer to naltrexone may be a function of motivation derived from being on methadone maintenance for at least 6 months.

These results seem to indicate that clonidine has a number of serious side effects and may not be any more effective than methadone detoxification. Clonidine's clinical use must therefore be carefully considered. The investigators are correct in indicating that the clonidine detoxification procedures were selectively disadvantaged in their protocol. They suggest that clonidine might be maximally efficacious when used as a rapid detoxification treatment.

Rawson et al. (1981) indicated that three meetings of the Committee on Problems of Drug Dependence have dealt with the uses of clonidine as an agent in the detoxification of opioid abusers. They further indicated that there is substantial public interest in the use of the drug, even though the extent of clonidine's clinical usefulness has not been fully determined. There is alleged to be sufficient data to indicate one specific use of clonidine: the rapid detoxification of patients receiving methadone and wishing to be inducted onto naltrexone. It is suggested that early voluntary terminations from naltrexone treatment programs may be a result of continued withdrawal symptoms. If clonidine can minimize withdrawal symptoms during detoxification from methadone, then Rawson et al. question whether naltrexone treatment is a necessary step in the transition from the chemotherapy of methadone maintenance to the drug free state.

Rawson et al. (1981) presented data from a collaborative study, comparing a group of patients receiving naltrexone with a group of patients receiving clonidine and naltrexone. Patients in the clonidine/naltrexone group were informed of the necessity of achieving a 10-day opiate free period in order to start naltrexone with no precipitated withdrawal symptoms. Patients in the clonidine-only group were informed that the 10-day opiate free period was extremely important if they were to successfully accomplish their detoxification from methadone and achieve opiate abstinence. Detoxification was achieved by an abrupt switch from methadone to clonidine.

Those patients participating in the clonidine-only detoxification study were encouraged, upon completion of the detoxification, to stay in drug free psychotherapy or accept a referral to a residential treatment program. Those patients participating in the clonidine and naltrexone detoxification study were encouraged, upon completion of the detoxification, to stay in postdetoxification treatment with naltrexone. This required clinic visits three times

a week. None of the patients at either facility were engaged in counseling or psychotherapy during the detoxification period.

Rawson et al.'s criteria for detoxification success in the above study were operationally defined as:

(1) the completion of a 10-day opiate free period following discontinuation of methadone; and

(2) the opiate use status of subjects 30 days post-methadone.

Nine of 12 (75 percent) in the clonidine/naltrexone group met the above criteria, as compared to three of 12 (25 percent) for the clonidine-only group. The differential efficacy of the clonidine detoxification procedure between the two groups did not appear to have been a result of differential symptom relief. Rawson et al. indicated that it appeared that, if the clonidine procedure was perceived by patients as being for a specific number of days with a clear goal and endpoint such as starting naltrexone, most of them could exert sufficient self control to abstain from opiate use for the 10 days postmethadone. Patients in the clonidine-only group did not have a clear endpoint. Seven of the 12 (58 percent) of the clonidine/naltrexone group patients were either on naltrexone or opiate free on day 30; three returned to methadone maintenance, two returned to illicit opiates, and one remained opiate free and not in treatment. This compared with only two of the 12 (16 percent) in the clonidine-only group who were opiate free on day 30; five had returned to methadone maintenance treatment, and five had returned to using illicit opiates.

One conclusion that may be drawn is that naltrexone can be extremely useful in preventing readdiction to opiates during the initial posttreatment period. Clonidine appears to be clinically useful when it is a portion of a comprehensive therapeutic plan. Detoxification by clonidine is not in itself a therapeutic endpoint. The initial post-methadone period is an extremely vulnerable period for recidivism. Rawson et al. did not address the need for counseling or supportive therapy during the detoxification and transition period, nor the reason why it was specifically absent from their study.

On the basis of Meyer and Sparber's finding (1976) that clonidine could block naloxone-induced morphine withdrawal in rats, Riordan and Kleber (1980) combined clonidine and naloxone in an attempt to accelerate the rate of detoxification from methadone. This accelerated detoxification procedure was initially undertaken in an inpatient unit. The procedure was as follows.

On day 1, the patient is pretreated with a total of 6 μg/kg, in three divided doses, 6-8 hours apart. The initial dose of 0.1 mg is used to assess the patient's responsiveness to clonidine.

On day 2, 11 μg/kg, in three divided doses, is administered. Naloxone 0.4 mg i.m. is injected every 2 hours, for a total of six doses, the first dose being 30 minutes after the first clonidine dose of that day.

On day 3, the patient receives 0.6 μg/kg clonidine in two doses at 8 a.m. and 2 p.m. Naloxone 0.8 mg i.m. is given every 2 hours starting 30 minutes after the first dose of clonidine.

On day 4, the patient is given 1.2 mg naloxone i.m. at 8 p.m., after his last dose of clonidine on day 3. If the patient demonstrates no withdrawal symptoms in response to this dose of naloxone, he is considered to be no longer tolerant to narcotic drugs, and other appropriate treatment, including narcotic antagonists such as naltrexone, may be started immediately.

Riordan and Kleber (1980) reported that they have successfully detoxified four patients using this technique. Three were users of at least 60 mg/day of heroin, and the fourth was a long-term methadone maintenance patient on 25 mg/day. The patients demonstrated a decrease in withdrawal symptoms after the second naloxone dose. The second day's naloxone produced minimal distress. Attempts to use this procedure on three outpatients remaining in the clinic all day and sleeping in their own residences at night were reported as unsuccessful. Effects of this protocol on vital signs, especially blood pressure, were not presented. Suggestions about the generality of this procedure were not given.

Gold et al. (1980a) presented data on 75 methadone maintenance patients (15-80 mg/day for a minimum period of 6 months) participating in an inpatient oral clonidine study that involved abrupt discontinuation of methadone

and administration of clonidine and a placebo after at least 36 hours of total abstinence. The study was randomized and double blind. Patients were excluded if they had a history of psychiatric or medical illness, though the number of patients so excluded was not presented. Clonidine (6 μg/kg) and a placebo were given orally in matching vehicles at 9 a.m. and 11 a.m. Clonidine, but not the placebo, caused a marked decrease in the signs and symptoms associated with opioid withdrawal. The onset of clinical relief was noted within 90 minutes of oral administration of clonidine. Significant relief from anxiety, panic, and subjective distress was reported. No indication was given as to whether these patients were continued on clonidine and completely detoxified or if they were then permitted to return to their methadone. No data on alterations in blood pressure were presented. No side effects were reported. Gold et al. presented the rationale for using clonidine in opioid withdrawal on the basis of a hypothesis of noradrenergic hyperactivity. They suggested that noradrenergic hyperactivity is responsible for the signs and symptoms of opiate withdrawal. Gold et al. also indicated that long-term exogenous opiate administration (methadone maintenance) might produce a decrease in the synthesis of endogenous opioid peptides (enkephalins) and alter receptor sensitivities at noradrenergic nuclei so that abrupt discontinuation of long-term opiate administration would result in a mismatch between needed and available opiate-mediated noradrenergic inhibition. Symptoms of opiate withdrawl would then result from a loss of inhibition-mediated "rebound" noradrenergic hyperactivity. They feel that the efficacy of low doses of clonidine in withdrawal supports the hypothesis of noradrenergic hyperactivity because these doses of clonidine have been shown in animal studies specifically to decrease noradrenergic activity and turnover. Low doses of clonidine are alleged specifically to decrease base-line noradrenergic activity in the brain and activity that has been stimulated pharmacologically or by opioid withdrawal. Gold et al. indicated that the above data on clonidine's effects on noradrenergic neurons also support the hypothesis that noradrenergic hyperactivity has a role in opioid withdrawal. Therefore they concluded that clonidine may be a useful, noneuphorigenic, nonopioid treatment for drug withdrawal and naturally occurring panic and anxiety states. No data were supplied to support the last conclusion.

Gold et al. (1979d) presented both an inpatient acute first-dose study and a 10-day inpatient study of 30 patients previously receiving methadone maintenance for a period of at least 6 months with an average daily methadone dose of 40 mg. All had unsuccessfully attempted detoxification in the past. All wished to be detoxified from methadone. The acute first-dose study was conducted on the patients 36 hours after they had been abruptly terminated from methadone. On the first day the patients received 6 μg/kg of oral clonidine or placebo in matched vehicles to demonstrate the effect of clonidine on opiate withdrawal signs and symptoms and to assess the changes in blood pressure produced by this dose. After the initial clonidine and placebo administration, patients without precipitous blood pressure declines were given clonidine 17 μg/kg/day, in divided doses, for at least 9 days. Clonidine dose was gradually decreased to 0 by day 14. All patients with a previous history of cardiac arrhythmias, hypotension, vasomotor instability, or psychiatric illness or hospitalization were excluded. All patients with a precipitous reaction to the test dose of oral clonidine were also excluded. No data are presented on the number of patients excluded in each of the aforementioned categories.

Oral clonidine 6 μg/kg produced a rapid and significant decrease in opioid withdrawal signs and symptoms for 6 hours. Systolic blood pressure decreased an average of 29 mm Hg and diastolic pressure decreased an average of 21 mm Hg at 120 minutes (131/91 to 102/70) and remained at this level for an additional 240 minutes. In two patients, systolic blood pressure was reduced to less than 60 mm Hg at 180 minutes after the first dose of oral clonidine. No indication is given as to whether the patients were supine, sitting, or upright when the blood pressures were taken. If they were supine, severe difficulties could be anticipated in routine daily activities. There were no significant changes noted in self-rating scales for energy or euphoria. There was a significant decrease in scores reported for the "uninvolved" and "angry" scales. All patients indicated that they needed their methadone prior to clonidine administration. Two hours after clonidine, no patient indicated he was experiencing any signs or symptoms of withdrawal. Placebo had no significant effect on any of these measures. The effect of the clonidine appeared to be independent of whether or not the patient had been receiving 15 or 50 mg of oral methadone per day.

All 30 patients continued with the 10-day study. A total of 12 μg/kg of oral clonidine was given on the first day (in two equal doses). For the next 9 days, 17 μg/kg/day of oral clonidine in three divided doses was administered. On days 11, 12, and 13, the clonidine dose was decreased by 50 percent. On day 14 no clonidine was administered; rather, all patients were administered naloxone 1.2 mg i.m. to assess for residual opiates or dependence. All naloxone tests were negative. All 30 patients completed the detoxification; none were using opioids 14 days later at time of discharge.

Clonidine doses were reported to have been decreased 14 times due to severe hypotension or sedation, but neither the number of instances of severe hypotension nor the severity of hypotension is presented. Twenty-one patients did complain of difficulty in falling asleep. Dry mouth, sluggishness, depression, and occasional bone pain were less frequent complaints. The exact incidence and prevalence of these complaints is not presented.

The negative effects associated with withdrawal, such as anxiety, irritability, and anger were rapidly reduced after clonidine administration.

Gold et al. concluded that clonidine is a useful agent in the rapid detoxification of opioids, as it permits patients to become opiate free long enough to initiate maintenance treatment with naltrexone. Clonidine is recommended for iatrogenic opioid addictions as well as for those patients maintained on methadone whose previous attempts to detoxify have been unsuccessful due to the morbidity of current slow detoxification practices. No data were presented for the last two recommendations, nor is any means suggested for determining which patients currently on methadone maintenance and requesting detoxification are most suitable for clonidine detoxification.

Uhde et al. (1980) conducted a double blind inpatient study of nine opioid-tolerant and opioid-dependent volunteers with methadone, placebo, and clonidine (6.0-26.9 μg/ kg/day) to determine whether early administration of clonidine could safely suppress the opioid abstinence syndrome without the emergence of withdrawal symptoms after clonidine was discontinued. This study was designed to evaluate the clinical efficacy and dose requirements of brief clonidine treatment for achieving a painless return to an opioid and drug free state.

All nine patients had had previous unsuccessful detoxification experiences. Seven were addicted to methadone, and two were addicted to dilaudid prior to their enrollment in a methadone maintenance treatment program. The range of methadone was 10-60 mg/day with a nine-patient average of 32 mg/day. The study's findings indicate that clonidine was as useful in suppressing or reversing the opioid abstinence syndrome for dilaudid addicted patients as for patients being detoxified from methadone.

No patient was reported as having had depressed respiration or serious bradycardia. The hypotensive effects are reported as being easily managed. Uhde suggested that clonidine detoxification should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure, and should not be used in pregnant women. Clonidine does not cross the placental barrier; therefore, it can precipitate a potentially fatal in-utero fetal-abstinence syndrome.

Kleber et al. (1980) indicated that clonidine is useful for withdrawal from methadone maintenance. They stated that it provides a more rapid alternative to the current detoxification procedures used with chronic methadone maintenance patients. The short detoxification period decreases the probability that the patient will abruptly terminate detoxification either to return to a higher dose of methadone or to illicit street drugs. Though the withdrawal syndrome is rarely life threatening, its symptoms are distressing enough to cause former addicts to return to their former addictions. This is offered as a partial explanation of why approximately half of all patients detoxifying from methadone voluntarily and abruptly terminate prior to reaching zero dose.

Kleber et al. indicated that over 100 patients had been successfully detoxified in their facility. They did not indicate how many patients prematurely terminated the clonidine detoxification. Data are presented on 10 patients only.

Kleber et al.'s recommended procedure for withdrawal from chronic methadone maintenance is presented in table 1.

Kleber et al. indicated that the above protocol could be shortened to 6 days and the dose of clonidine reduced somewhat in treating withdrawal from the shorter-acting narcotics such as heroin, dilaudid, or Percodan.

They recommended tolazolidine, a clonidine antagonist, as well as intravenous fluids, to treat prolonged clonidine-induced hypotension.

Kleber et al., in preliminary results on a small sample of patients evaluated 6 months after clonidine detoxification, suggested that almost half of the patients have returned either to methadone maintenance or to illicit opioid use. However, no sample size is presented.

Charney et al. (1981) assessed the treatment of methadone withdrawal with clonidine in 25 patients (21 males) to establish effective dosage guidelines and to examine effects on specific signs and symptoms of withdrawal under controlled inpatient conditions. This is the first report on the effects of clonidine on cardiovascular function during withdrawal.

The patients had been maintained on methadone for at least 2 consecutive years prior to study participation. Clonidine was administered, in three divided doses, after a 48-hour period of abstinence from opioids. Additional clonidine doses were given at other times, as required by the presence of withdrawal signs or symptoms. The first two clonidine doses were 5 μg/kg. Clonidine was withheld if the standing blood pressure was less than 85 mm Hg systolic. Twenty of the 25 patients (80 percent) completed treatment. They completed the protocol and were taking neither clonidine nor methadone at the time of discharge from the inpatient unit. The five patients reported as not completing the study were all unable to deal with being on a locked inpatient ward. None of these patients completed more than 3 days of the study.

The peak daily ranges of clonidine were 10-25 μg/kg/day. Patients were tapered off clonidine during a 3- to 4-day period. No recurrence of symptoms was noted. Clonidine was equally effective in treating the withdrawal signs and symptoms in patients who were opioid abstinent for either 24 or 48 hours from the last methadone dose. Clonidine did not completely protect all patients from all the signs and symptoms of opiod withdrawal. Anxiety, restlessness, insomnia, and muscle aches continued to be reported during the detoxification experience. More than half of the patients reported these signs and symptoms on two of the three checklists on the day #5. At discharge, most patients were reported completely asymptomatic. The actual numbers were not presented.

Table 1. Recommended procedure for withdrawal from methadone maintenance

Day	Dose
0	Usual dose of methadone
1	Clonidine: 6 μg/kg as test dose 6 μg/kg as bedtime dose Note: A smaller and less frequent dosage of clonidine is used on the first day because the long-acting nature of methadone leads to less severe withdrawal symptoms on this day.
2-10	Clonidine: 17 g/kg divided as follows: 8 a.m. - 7 μg/kg 3 p.m. - 3 μg/kg 10 p.m. - 7 μg/kg[a] In general, the peak drop in blood pressure has occurred by 2 or 3 hours after the clonidine dose. It may be necessary in the presence of persistent hypotension or excessive sedation to reduce the clonidine dose. Additional prn. doses of clonidine may be given up to 0.4 mg/day, divided into two to four doses.
11	Clonidine: 8 g/kg divided as follows: 8 a.m. - 3 μg/kg 3 p.m. - 1 μg/kg 10 p.m. - 4 μg/kg
12	Clonidine: 4 g/kg divided as follows: 8 a.m. - 2 μg/kg 10 p.m. - 2 μg/kg

Table 1 (continued)

Day	Dose
13	Clonidine: 2 μg/kg at 8 a.m.[b, c]
14	No clonidine

a Higher dosage is used at bedtime because of the frequency of insomnia as a withdrawal symptom not totally controlled by clonidine. If systolic blood pressure drops below 90 or diastolic below 60 mm Hg, the clonidine dose may be withheld until the pressure rises and the patient put at bed rest in the supine position.

b Although rebound hypertension does not usually occur even with abrupt clonidine cessation until it has been used for 30 days, we have tapered its use as a precaution.

c If the patient is to be started on a narcotic antagonist such as naltrexone, it would be useful to check at this time for residual opiate dependency by giving naloxone, i.m. or i.v., 1.2-2.0 mg.

The maximum doses of clonidine were reported as having statistically significant but clinically negligible effects on sitting systolic and diastolic blood pressures and on sitting and standing pulse rates. Nineteen of the 20 patients (95 percent) had at least two doses withheld because systolic standing blood pressure was less than 85 mm Hg. No syncopal episodes were reported, though most patients apparently complained of lightheadedness upon standing. Blood pressures rose, without rebound, when clonidine doses were decreased. Sedation to the point of impairment was noted during the first few days on clonidine. Dry mouth and constipation also were reported by the patients.

Charney et al. stated that 7 days of clonidine given three times a day, totaling 16 μg/kg, with the dose tapered to zero over a 3- to 4-day period, should enable most patients to withdraw successfully from moderate doses of methadone. The recommendation was made that patients be

gradually titrated to methadone levels in the 20-40 mg/day range prior to detoxification. Clonidine significantly lowers blood pressure during its first 7 days of administration; 15 mm Hg decreases in systolic and 10 mm Hg in diastolic pressure were recorded. Charney indicates that patients should be evaluated on a daily basis.

Charney also stated that there may be several possible explanations for the incomplete suppression of withdrawal symptoms of clonidine. It is hypothesized that clonidine acts at inhibitory alpha-two adrenoreceptors to decrease the severity of symptoms and signs of opioid withdrawal by moderating the increased noradrenergic activity induced by opioid abstinence. Thus, the doses of clonidine which may be given safely may not adequately inhibit noradrenergic activity in some of the subjects. Another hypothesis is that alterations in other neurotransmitter systems not suppressed by clonidine may be responsible for some of the clinical signs and symptoms. Recent animal studies by Llorens et al. (1978), Hamburg and Tallman (in press), and Nathanson and Redmond (1981) indicate that chronic opioid administration increases the number of both alpha-two and beta adrenoreceptors and/or increases the sensitivity to these receptors. These changes may contribute to symptom development and reduce the effectiveness of clonidine. Severe withdrawal might alter brain mechanisms and lead to a secondary abstinence syndrome and other symptoms. More research with clonidine needs to be conducted in controlled inpatient and outpatient studies by clinical investigators who are knowledgeable about the pathophysiology of clonidine and opioid abusers.

Charney and Kleber (1980) report a single case of a woman addicted to oxycodone combination (Percodan) as a result of chronic bladder pain. She was successfully detoxified, as an inpatient, on oral clonidine, on the regimen presented in table 2. At the higher doses of oral clonidine, her standing blood pressure decreased from 120/80 to 90/60. Upon discharge she was normotensive. Her oral chlordiazepoxide hydrochloride (10 mg tid) was not altered during this study.

Charney and Kleber's clonidine dosage schedule to detoxify patients with an iatrogenic opiate addiction is as follows:

A tid dose appears to be adequate since a single dose of clonidine can eliminate the opiate abstinence syndrome for 240-360 minutes. There are two significant applications of this protocol. First, it may be used in conjunction

Table 2. Detoxification regimen for iatrogenic opiate addiction

Hospital Day	Clonidine (mg) 8 a.m.	3 p.m.	10 p.m.	Total
1	Normal level of self-medication of opiate			
2	.1	.1	.2	.4
3	.3	.3	.4	1.0
4	.3	.3	.3	.9
5	.3	.3	.3	.9
6	.3	.3	.3	.9
7	.2	.2	.2	.6
8	.1	.1	.1	.3
9	.1	0	0	.1

with psychotherapy for those individuals addicted to opioids who do not have a physical basis for the pain; and second, it may be used for patients with painful physical disease. Periodic clonidine detoxifications may provide more effective analgesia by temporarily reversing the tolerance developed with long-term narcotic use. Fielding et al. (1978) have shown that in animals clonidine has analgesic properties similar to those of morphine. McCleary and Leander (1981) proposed that clonidine induces analgesia as measured by tail withdrawal by different mechanisms than it induces suppression of fixed-ratio responding. Their results suggest that stimulation of postsynaptic alpha-adrenoreceptors is a significant component of clonidine-induced analgesia, whereas the behavioral suppression is mediated by presynaptic receptors on noradrenergic neurons or by adrenergic receptors. Therefore, it could be postulated that these patients may not complain of pain during the detoxification. Future studies are necessary to determine the validity of this hypothesis.

Washton and Resnick (1981) reviewed the literature on the single dose and inpatient and outpatient studies using clonidine and lofexidine in the detoxification of opioid dependent patients. While no new patient data were presented, the review does consolidate a number of important findings about the usefulness and limitations of clonidine and lofexidine. Clonidine does have a role in the withdrawal regimens of patients wishing to become free of either methadone or other opioids. However, the principal side effects of hypotension and sedation and the less troublesome side effects of dry mouth and dizziness will limit clonidine's general acceptance by patients and clinicians.

SUMMARY OF THE CLINICAL FINDINGS

There have been a number of rather diverse research and clinical studies on the efficacy and safety of clonidine for the detoxification of opioid addicted patients. Clonidine has proved to be useful for the detoxification of patients who have been stabilized on relatively low doses (less than 40 mg and preferably less than 20 mg) of oral methadone. It has had less clinical utility in the detoxification of street heroin addicts. Isolated reports of clonidine detoxification of iatrogenic addictions to shorter halflife opioids have demonstrated another application for this nonopioid.

The difficulties with clonidine are neither unique nor unpredictable. Clonidine has an approved NDA. The research activities utilizing this drug are relatively few. The clinicians indiscriminately using this drug are many. The latter statement is based on the number of phone calls this reviewer has received from physicians who, without any apparent understanding of either the antihypertensive or the sedative effects of the drug, wish to know the detoxification schedule for the use of clonidine in an outpatient setting. Many clinicians do not understand that special knowledge and experience are necessary to achieve successful detoxification of opioid addicts.

Internists and psychiatrists seem to accept clonidine as another drug in their armamentarium that will assist in the cure of opioid addiction. Many apparently are collecting the various detoxification schedules that appear in the literature and implementing them. While no clonidine detoxification-related deaths have thus far been re-

corded in any of the research reports reviewed, it is only a matter of time before they will occur.

Hunyor et al. (1975), Conner and Watanabe (1979), Neuvonen et al. (1979), and Anderson et al. (1981) have published their accounts of managing clonidine overdoses. The toxic effects of abrupt cessation after the prolonged administration of clonidine are well described by Hansson et al. (1973). Acute psychotic and other severe psychiatric problems have been recorded after clonidine detoxification. Hypotension is well documented even in healthy addicts. Sedation is a frequent side effect that causes discomfort and potential hazards if the patients are operating automobiles or other machinery. A black market already exists for clonidine. It is easily diverted. It is not a controlled substance. An increased morbidity and mortality from the inappropriate street use of this drug can be anticipated. Clonidine is not a cure for opioid addicts; it may be a component of some detoxification regimens. It is possible that the revolving-door phenomenon experienced with methadone detoxification may be replicated in those treatment progams. Is clonidine's recommended use as an alternative to methadone for the detoxification of opioid addicts worth the potential consequences? Time and future reports in the medical literature and lay press will answer this question.

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CRITIQUE

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INTRODUCTION

In 1523 the philosopher Erasmus noted, "In regione caecorum rex est luscus." In spite of the many good points of Dr. Ginzburg's comprehensive review, he neglected to pay suitable attention to this important observation. For those of you whose Latin is rusty, the quote simply means, "In the kingdom of the blind, the one-eyed man is king." Dr. Ginzburg is so preoccupied with the possible problems of clonidine and its misuse by doctors or addicts that he loses sight of the real problems associated with other methods of detoxification, and he does not note sufficiently the advantages of clonidine over methadone detoxification. I shall return to this point later.

The review by Dr. Ginzburg is a thorough one of the American literature that has emerged since the original Gold, Redmond, and Kleber reports in 1978 (Gold et al. 1978a; 1978b). It would be pointless for me to add anything to his summary of those studies. Before going on, however, I would like to mention some additional studies which he may not have had available to him, either because they were published in Europe or have been accepted for publication in this country but are not yet out. A recent paper from Denmark by Andreasen et al. (1981) described the use of clonidine to detoxify 10 narcotic addicts. All 10 were detoxified within a period of 4 to 6 days. All 10 clients had previous experience with methadone detoxification and stated that they preferred the clonidine procedure. The authors concluded that in their limited study clonidine was an effective detoxification agent. The study was neither blind nor placebo controlled and, therefore, its conclusions can be at best supportive rather than definitive. The dose of clonidine used was .15 mg four times daily for 6 days. Seven of the 10 found they did not need clonidine after the fourth day of the 2-week residential stay; two clients took two extra clonidine tablets the first 2 days. The study was carried out not in a hospital but in a 14-day stay in a rented farmhouse where one physician and two rehabilitation workers lived with the clients on what they called "a detoxification trip." An interesting note was that there was a bottle of clonidine

tablets in the open on the table during the entire 2 weeks without any attempt by the individuals to take more than has just been described.

A recent study from Italy by Fantozzi et al. (1980) described the use of clonidine to block naloxone precipitated withdrawal which is used to test whether individuals are physically addicted and, therefore, eligible for a methadone maintenance program. The study was single blind with patients being given either morphine or clonidine when abstinence signs and symptoms appeared. There were 10 patients in each group. It was found that clonidine was as effective as morphine in suppressing the withdrawal symptoms, but the time course of the clonidine action was slower than the morphine. The clonidine dose used was an initial i.v. dose of 150 μg followed by an oral dose of 5 μg/kg twice daily. Of the 10 patients in each group, one in the clonidine group had to be discontinued because of the appearance of sinus bradycardia (below 50 beats per minute after 9 hours). Another one of the clonidine patients was discontinued when abstinence signs and symptoms reappeared with increasing severity from the 23rd hour onward. In general, clonidine tended to lower the heart rate much more than morphine although it did not approach statistical significance. Of interest considering its hypotensive effect, there was no significant difference between the blood pressures of the patients in either the morphine or the clonidine cells.

A study by Pettibone and Mueller (1981) showed that clonidine increases beta endorphin levels in rats, an intriguing finding in view of the fact that clonidine-induced analgesia, as Dr. Ginzburg pointed out, is not reversed by naloxone. A recent paper by Hoder et al. (in press) from New Haven will appear in the New England Journal of Medicine. It gives case histories of the successful use of clonidine in treating withdrawal symptoms in two newborns of methadone maintained mothers. The clonidine method was seen as preferable to the previous methods used at Yale-New Haven Hospital in treating such withdrawal.

The rest of this paper will be spent discussing the areas that had been assigned for review, adding to Dr. Ginzburg's paper our additional clinical and research experience.

Appropriate Dosing Regimens

Ginzburg has summarized the dosage regimens used in the various published studies. Some additional comments are in order since our clinical experience does not always come through clearly in the literature.

We have learned it is easier to give large doses and suppress withdrawal than to try and catch up to patient symptoms. When we tried to increase gradually the clonidine dose to match the intensity of withdrawal, patients were much more uncomfortable and the dosage of clonidine needed was ultimately higher. This is similar to the English finding that it is easier and takes less overall narcotic in chronic pain patients to prevent pain or suppress it when it first appears than to suppress it at its peak.

There are important differences between dosing regimens on an inpatient and outpatient basis. On an inpatient basis where one does not need to worry about sedation, the patient can be started on relatively high doses at once. Also one can give the clonidine every 4 to 6 hours, which will produce a maximum antiwithdrawal effect. On an outpatient basis the problem is as follows: one wants to start as low as possible in order to minimize initial sedation which can interfere with a patient's functioning. But once a patient has developed some tolerance to the sedative effect, one needs to quickly shift the dose upward to avoid the withdrawal symptoms. The transition, if not properly done, may lead patients to drop out either because of complaints about the sedation or because of complaints that the drug is not adequately preventing withdrawal. Currently, our outpatient procedure is to start the first day with 0.1 mg tid, increasing to a total of 0.4 on day 2, no more than 0.4 to 0.6 on day 3, 0.6-0.8 on day 4, and 0.8 to 1.0 from day 5 on. It is very important to warn patients about the sedative effects likely to occur in the first 48 hours or so and to caution them about driving a car or operating hazardous machinery. We have tried to insist in New Haven that patients have a ride from the clinic the first day. Using the above techniques along with the supports described later, we have nearly doubled the success rate reported by Washton and Resnick in their outpatient study (1981).

There is no need for very high doses on the first day of methadone withdrawal because the peak intensity of symptoms does not occur until much later on. When dealing with short-acting narcotics, however, such as heroin, morphine, or dilaudid, I have found it necessary to go as high as 1.5 mg of clonidine on the first day. The latter dose was used on a patient with an iatrogenic habit of 120 mg morphine a day.

Continued narcotic use by the patient during withdrawal appears to diminish the effectiveness of clonidine, but precise data as to the magnitude of the effect are not available yet.

Patient Characteristics

As Dr. Ginzburg noted, there is a need to screen patients for preexisting serious psychopathology. Where we have not done so, we have found an increased incidence of serious depression or of psychosis immediately following the clonidine (Gold et al. 1979). It is not clear whether this is due to the stress of the abrupt withdrawal, a clonidine effect, or a reemergence of existing pathology due to the loss of the methadone "normalizing" effect on an abrupt basis. All the patients in our series who have gotten into trouble have had a previous history of serious psychopathology. This area needs further exploration partly to improve selection methods for clonidine, but more importantly because of what it may tell us about the relationship of exogenous and endogenous opiates to the variety of psychiatric symptoms (Watson et al. 1979).

Duration of Treatment

Our experience has indicated that there is no need for longer than 14-16 days of clonidine in detoxification from methadone maintenance and no more than 6-9 days with shorter-acting narcotics. There does not appear to be any advantage gained by prolonging the clonidine regimen beyond these times. We have not noted the possible disadvantage of rebound hypertension when the period of time has been kept to these intervals. As Rawson et al.'s (1981) study stresses, patients who know they are going to naltrexone may do better in terms of remaining drug free than those for whom the goal of clonidine is simply to remain drug free.

Support Services

Narcotic addiction is clearly both a psychosocial and physiological condition. The high percentage of Vietnam veterans addicted to heroin while in Vietnam who were not addicted a year later when back in the United States, as well as the overwhelming majority of medically addicted individuals who cease narcotic use once the underlying painful condition is treated, all bear witness to the important role of psychological and social factors. Conversely, the existence of the opiate receptor sites, the endorphins, and the protracted abstinence syndrome are significant reminders of the potential role which biologic factors play. Our clinical experience with clonidine to date supports the necessity of adequate psychological support during and after the withdrawal process. Patients usually have been on a daily drug, whether heroin or methadone, for many years. Sudden cessation of this daily drug intake around which many patients daily activities were organized is often felt as an acute loss or disorienting factor with resultant depression, confusion, and finally return to drug use. We have learned through painful experience that during clonidine administration, patients should have a daily opportunity to talk about what they are going through with a knowledgeable clinician, and they should remain in treatment for at least 1 to 3 months afterwards. Where the size of the program permits, it may be useful to establish a clonidine group (or postwithdrawal group regardless of detoxification method) where patients can meet at least once a week to discuss with a skilled group leader the problems and the psychological loss involved in remaining abstinent. Although this support can be crucial, it is too often spurned by patients who feel that once they are clean, they want no further program contact.

In our current outpatient clonidine study, each patient is seen daily by both a nurse and a psychiatrist who are blind to whether the patient is on clonidine or gradual methadone withdrawal. Their findings, plus the blood pressure which is taken by an open nurse, is reported to a second psychiatrist who then prescribes the clonidine dose without seeing the patient, so as to preserve the blind as well as possible. The experiences we have had with different staff in the blind role have, again, emphasized to us the importance these individuals play in being able to help patients remain in treatment. This support is especially crucial during the first few days when sedation can be very discouraging and leads the patient to want to drop

out, later in the week when the patient may feel distressed by the presence of withdrawal symptoms not totally blocked by clonidine, and during the placebo period when craving may be high.

Use with Other Treatment Drugs

Dr. Ginzburg pointed out that tricyclic antidepressants have been shown to block the antihypertensive effect of clonidine. We have noted clinically that use of such drugs may interfere with the withdrawal suppressing effect, and they should therefore be avoided. The primary drug that we add to the clonidine regimen is for sleep, since insomnia is the most important withdrawal symptom not suppressed by the clonidine. Insomnia may also be worsened by clonidine, which decreases REM sleep (Jimerson et al. 1980). We have used either chloral hydrate, 0.5-1 g, or flurazepam, 30 mg at night, and both have been effective in dealing with insomnia. Putting the patient on naltrexone after clonidine detoxification is not always possible, either because the drug is not available or the patient is not willing. Where we have used it, it appears to improve the likelihood of remaining drug free and, interestingly enough, to prevent the reemergence of any later withdrawal symptoms.

Side Effects

In the over 100 patients I have personally treated with clonidine, either in a blind research protocol or in open studies, I have not seen, other than the psychological problems described earlier, any serious side effects. The major problem has been sedation, while other symptoms such as dry mouth have been annoying but not serious. Hypotension, in general, has not been a serious problem for either our inpatient or outpatient studies. In general, if the blood pressure is low with the high doses used by inpatients, delaying the dose for a few hours, skipping it altogether, or diminishing it have all been satisfactory ways of resolving the situation. Such steps are rarely necessary after the first 48 to 72 hours.

DISCUSSION

Dr. Ginzburg has stressed that clonidine is not a cure for opiate addiction, it is a detoxification treatment. I could not agree more, and would only want to add that I am not aware that any of the papers he has cited feel that it is a cure. Clearly it does not prevent relapse once the patient is clean. To the extent, however, that more individuals can get to zero dose with clonidine than with gradual methadone withdrawal, it can increase the number of individuals able to remain clean, if the percentage of abstinence remains constant.

Dr. Ginzburg is appropriately concerned about the misuse of clonidine by physicians, programs, and patients. I could add a number of horror stories to his, such as a methadone program in the Washington area which has given its clients a large number of clonidine tablets when they reach 15 or 20 mg of methadone, and told them to use the tablets as needed for unpleasant withdrawal symptoms. Patients have arrived in my office from cities all over the United States carrying bottles of 50 or 100 clonidine tablets, usually given not by ignorant physicians but by well meaning ones who meant to help the patients with their narcotic withdrawal. The way to treat this is the same as with other potent medications in the physician's armamentarium, namely, improved knowledge rather than proscription.

Proscription has not been a terribly effective tool in the narcotic problem in general in the United States, and although Ginzburg does not advocate this with clonidine directly, there is almost an intimation of it. I agree that we have been fortunate that black market use has not led to any fatalities, since large overdoses can cause death, and the sedative effects can lead to auto accidents and injuries. On the other hand, street methadone has been associated with numerous fatalities, and Dr. Ginzburg would be the first to agree that this does not mean that we should close down methadone maintenance programs. It means that we must do our best to educate programs and dispensers as well as potential patients about the hazards involved, and we must use appropriate safeguards to minimize diversion.

Dr. Ginzburg is also concerned that special knowledge and experience is necessary to correctly handle the clonidine procedure. Again, I agree with him. In inexperienced or

unskilled hands, especially on an outpatient basis, the procedure may not be satisfactory, especially in the transition period mentioned earlier between keeping the dose low enough to avoid excessive sedative effects, and then raising it at the right time to avoid withdrawal symptoms. Such a finding, however, is not unique in medicine. Especially with new procedures, physicians often have to learn the most appropriate ways of performing them. The role of researchers is to try to develop as simple a procedure as possible within the limits of the technology as well as to search for new drugs that may have the same beneficial effects with fewer side effects. That has occurred in many other areas of medicine and should certainly occur in this one. The most important ultimate effects of clonidine may be the opening up of a new area of research into the mechanism by which withdrawal is mediated in the brain, thereby leading to even better treatments for both maintenance and withdrawal as well as treatment of the protracted abstinence syndrome. We are currently experimenting with a number of procedures which might improve the clonidine method. Lofexidine may be a drug that is an improvement upon clonidine, although the evidence I have seen to date leaves me unconvinced.

CONCLUSION

Detoxification from opiates has probably been a problem for as long as drugs have been available for the relief of pain or the production of euphoria. Although the withdrawal syndrome is rarely life threatening, its symptoms are often distressing enough to make it difficult for many addicted individuals to cease using drugs, and a chronic persistence of low level symptoms has undoubtedly been a contributing factor to early relapse. The cures proposed over the last 100 years have at times been worse than the disease, either introducing drugs which are even more addicting, or using other methods that may cause even more distress or, at times, a significant mortality rate.

At the turn of the century, detoxification was often equated with cure. Nowadays we hopefully are more sophisticated, realizing that detoxification is only one step, albeit an important one, in the whole chain of ultimate success in treatment. Because of the problems that previous new methods for detoxification have produced, however, it is important that anyone who introduces a new detoxification method should view it with humility. The research

field should view it with skepticism until both its efficacy and safety have been thoroughly proven. While the studies to date on clonidine appear to have indicated its safety and its efficacy in experienced hands on an inpatient basis, its place in our armamentarium will probably rest ultimately on outpatient use. Its efficacy there is, as yet, not clearly shown.

In concluding, however, I would like to return to the quotation with which I started this paper. Detoxification is not in the same blind state it was 50 years ago, and gradual methadone withdrawal is certainly an improvement over earlier methods in many ways. However, since the success rates of withdrawal from methadone maintenance are usually under 50 percent, detoxification is still more blind than sighted. In this kingdom, clonidine may be analagous to the person with one eye.

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DISCUSSION SUMMARY

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The primary focus of the discussion was the safety and efficacy of clonidine as an opiate detoxification agent. There was general agreement that clonidine effectively ameliorated some, but not all, symptoms of opiate withdrawal. However, as the abstinence syndrome becomes more severe, larger doses of clonidine are required to control the withdrawal symptoms and clonidine toxicity may result. Since there is a point at which the side effects of clonidine preclude increasing the dose, its utility is limited by the level of narcotic dependence.

There was some discussion as to whether enough research has been done and whether the existing data suggest that clonidine is safe and effective as a detoxification agent. There was no agreement on this issue. The reasons for the lack of consensus were primarily related to the question of safety of the drug. Not infrequently, patients experience side effects at doses used to treat hypertension. Doses larger than those used to treat hypertension are often required to ameliorate opiate withdrawal symptoms. The major side effects discussed were orthostatic hypotension, sedation, and insomnia. It was noted that tolerance appears to develop rapidly to the sedative effects. Some of the participants expressed concern about the dysphoria (psychosis and/or depression) which has occurred while the patients were either receiving clonidine or subsequent to its termination. In addition some concern was expressed about using clonidine for a currently unapproved indication. While the physician has the legal right to use an approved drug for an unapproved indication, he or she is at risk for a malpractice suit if, in doing so, clonidine's potentially dangerous side effects become manifest.

Two of the participants (Kleber and Resnick) have been active in clonidine research. Dr. Kleber expressed the opinion that the drug's efficacy has been demonstrated and outlined protocols for its use in both detoxification from methadone maintenance and other opiate addictions. Data from Dr. Resnick's controlled double blind study indicated that clonidine was no more effective than 1 mg/day decreases in the dose of methadone in helping outpatients

reach zero dose. Dr. Kleber disagreed; his studies indicated that clonidine may be more effective. Dr. Klein noted that there were a number of reasons why a nonnarcotic such as clonidine might be more acceptable if it were proven safe and efficacious for this indication. Dr. Resnick suggested that clonidine may be most useful as part of the induction procedure for naltrexone treatment and for those individuals for whom methadone treatment was either unavailable or undesirable.

There was a brief discussion about the use of another alpha-2 agonist, lofexidine, for detoxification from narcotic addiction. This drug is currently not marketed in the United States. It is only available under an IND exception. Dr. Resnick indicated that he has used lofexidine for this indication in a small number of patients. There have been fewer side effects with lofexidine, and lofexidine was as effective as clonidine in ameliorating withdrawal symptoms. Some of the participants speculated that side effects similar to clonidine's may occur with lofexidine as the dose is increased to treat individuals with more severe withdrawal symptoms.

Most participants agreed that it would be desirable to have nonnarcotic agents available to detoxify opioid dependent individuals. Clonidine, lofexidine, and other alpha-2 agonists with fewer side effects may eventually serve this purpose. Research to develop such a drug was considered a high priority.

CHAPTER 7. USE OF D-PROPOXYPHENE AS A MAINTENANCE OR DETOXIFICATION AGENT FOR OPIATE ADDICTS

Edward Senay, M.D.

INTRODUCTION

With the possible exception of psychotherapy, methadone maintenance treatment of heroin addiction has been examined critically as much as or more than any other human service modality in history.

The preponderance of evidence suggests strongly that while in maintenance treatment, addicts use fewer illicit drugs and commit fewer crimes. More modest but still positive changes are seen in employment and psychosocial functioning. In addition, evidence suggests that time in treatment is related positively to posttreatment changes in these outcomes (Sells et al. 1978). Despite such changes in groups entering treatment, there are individuals whose needs and preferences might be better served by a drug which would produce a less severe degree of dependence and a milder and hence more manageable withdrawal syndrome. D-Propoxyphene and more particularly its napsylate (PN) possess the pharmacologic properties of producing a low level of dependence and a mild withdrawal syndrome and appear therefore to be logical drugs to explore to improve narcotic withdrawal and narcotic maintenance therapy.

The ground for testing this drug was particularly fertile in Los Angeles, which had community hesitation without parallel in the United States concerning methadone maintenance.

CLINICAL REPORTS

Tennant reported in 1973 the first experience with the use of PN as a detoxification and maintenance agent (Tennant 1973a). PN was administered to 102 inpatient heroin addicts over 5 days. The initial daily dose of PN was 1600 mg given in two to four doses. Sixty-four of the 102 inpatients were successfully detoxified, as verified by a urine test negative for opiate drugs 7-10 days

following completion of the 5-day detoxification regimen. Mild sedation and slurring of speech were the only side effects observed in these 102 inpatients.

In this report Tennant also presented additional observations of 38 heroin addicts detoxified as outpatients with a 5-20 day detoxification regimen with initial daily PN doses of 1000 to 1400 mg. Fifty percent of patients completed this regimen. Hallucinations, not further described, were reported in two patients.

In this report Tennant also cites experience with 16 outpatients maintained with a single oral daily dose of PN for a mean of 45 days. Doses ranged from 600-1400 mg. Nausea, slurring of speech, a "high," and sedation were side effects in some patients, with the specific percentage not presented.

In a separate 1973 report in JAMA, Tennant cites experiences with 280 heroin addicts who were detoxified on PN (Tennant 1973b). This paper is apparently presented in more complete form by a third 1973 report in which Tennant states that, of 280 heroin addicts detoxified with PN, 230 were detoxified as inpatients with a success rate of 83 percent, and 50 outpatients were detoxified with a success rate of 62 percent (Tennant 1973c). The regimen used was similar to that reported in his first 1973 report, but a little larger dose was used. A successful detoxification was defined by history and a urine negative for opiates.

In addition to these quite impressive detoxification statistics, Tennant mentions an experience with 92 patients maintained on PN for a mean of 85 days. Mean maintenance dose was "800-900 mg per day" with a range from 400 to 1500 mg. Tennant mentions "common side effects of dysphoria, mild visual hallucinations, sedation, and slurring of speech." These side effects were reversible with decrements in dose.

In 1974 Tennant reported on his continuing experience with PN. His 1974 assessment of the work reported in JAMA in 1973 was as follows: "Initial results indicated that PN would detoxify and maintain most individuals who are physically dependent upon heroin" (Tennant et al. 1974). This statment apparently refers to the inpatient success rate of 82 percent in detoxification and the 62 percent success rate in outpatient detoxification. The

ability of PN to maintain "most individuals" is much less apparent in his subsequent reports.

In the 1974 report Tennant cites a figure of 370 inpatients who have been detoxified. It is noteworthy that the dose of PN employed on day 2 of the detoxification regimen was 1400 mg, and that Tennant observed "no significant side effects." The figure of 370 inpatients is not further broken down. This raises an important question: did all 370 patients complete detoxification or were they the successes of some larger group? Tennant added that 30 patients had been detoxified on an outpatient basis using a 5-day PN withdrawal regimen. Again, the assumption is that all 30 were detoxified, but they may and probably did represent the successes of some larger but unreported number of subjects.

Tennant next reports an experience with outpatient short-term maintenance with PN. One hundred patients were maintained from 22 to 240 days on daily doses ranging from 400 to 1600 mg. Maintenance doses were given in a single oral dose. Also in this report is a brief description of eight patients who were withdrawn from methadone abruptly, then placed on PN. All became abstinent after periods of maintenance on PN of 10 days to 5 months. Without a more detailed description of these studies, critique is difficult. At face value, Tennant is reporting on eight cases, all apparently successful in reaching abstinence from methadone (high doses of methadone in half the cases) utilizing a withdrawal regimen of PN. We do not know if urine studies were carried out in these cases, so we do not know of the use of other drugs, alcohol, etc.

Again, the studies reported in the 1974 paper were reports of clinical experiences and not studies in the sense of systematic examinations designed to measure various outcomes via randomly assigned samples under double blind conditions. Clinical reporting was evident when Tennant administered a questionnaire on the effects of PN to 24 patients who had taken PN for 30 or more continuous days. He describes them as "high dose" patients although we do not know the dose level of any individual nor do we learn what was the mean dose of the group. In any event 42 percent reported an unpleasant high, and 33 percent reported hallucinations. Presumably these patients were drawn from the maintenance group; if so, then we know that their PN dose was built up gradually. If this is so, then it appears that the elimination of serious side

effects such as hallucinations is not very effective by the slow buildup of dose. Seizure-like or frank seizure activity was not asked for in this group's questionnaire, an important omission. One cannot generalize from this group because we do not know how the group was selected. Finally, in this 1974 set of studies, 14 patients monitored for over 90 days showed slight increase in lymphocytes and in cholesterol.

The foregoing report adds in numbers and therefore begins to establish that in usual clinical practice PN appears to be acceptable to many addicts and, at least in the short term, is relatively safe. But because of a lack of random assignment and double blind controls these studies tell us nothing about efficacy.

Reports of clinicians in centers other than Los Angeles were presented in a paper by Inaba et al. (1974). This single paper reports on clinically successful use of PN for detoxification in 178 patients (Bergin), 80 patients (List), and 32 patients (Inaba et al.). In the Bergin section of this paper, addicts were withdrawn as inpatients using a 5-day PN schedule. PN was given 100 to 200 mg four to six times a day. We are not given any data on those not finishing the detoxification regimen. It is highly unlikely that 178 addicts started and finished a 5-day detoxification; again the 178 appears to represent the successes from some unspecified starting number.

List's report is of interest because of the concurrent use of PN in patients being incrementally detoxified from methadone, while a second group studied by List was withdrawn on methadone alone. Apparently there were no negative interactions between PN and methadone, and the PN-assisted methadone detoxification group had 33 percent successfully detoxified versus 6 percent of the methadone-alone group. But we do not know if patients were randomly assigned to the study groups, and there is no mention of serious side effects.

Inaba et al. studied PN in 32 patients at the Haight-Ashbury Clinic. All were heroin addicts and difficult management cases. PN was given twice a day for periods of 5 to 30 days. About half reported heroin use during detoxification, and 90 percent reported that PN relieved their heroin yen. Four of the 30 reported "a psychotogenic drug-like reaction," and two reported "jitteriness," so that the side effects seen in other studies

were apparent. The occurrence or nonoccurrence of convulsions or seizure-like activity was not asked for nor were these problems mentioned by any of the authors of this joint report, a curious omission in view of the citation of Tennant's 1973 work.

These studies add to the evidence of acceptability but again do not address the question of efficacy because of lack of experimental design. List's use of concurrent PN and methadone was the first mention of what would appear to be an obvious detoxification regimen to explore.

Tennant et al. (1975a) reported on 28 patients seeking to withdraw from methadone maintenance. One group was lowered to 40 mg methadone daily and then given PN in divided doses of 600 to 1400 mg daily. When methadone was discontinued PN was withdrawn "within two to four weeks." The authors do not specify if this was a sudden or gradual withdrawal of PN. A second group was transferred directly to PN while abruptly ceasing methadone. The author says without further comment, "This was easily accomplished when the methadone dose was 30 mg per day or less." We do not know the doses of methadone in the two groups nor do we have an account of any failure in the second group because of an initial methadone dose greater than 30 mg. Apparently the study subjects were not assigned randomly, so generalization of the findings is not possible. Seventeen of 30 patients achieved a drug free state. The authors do not report if these two methods had equal numbers, and it is not possible to link these two methods with the outcomes because outcomes are reported for the whole 28. The surprising finding was that 60 percent achieved abstinence. Eight study patients apparently could not withdraw from PN after they completed methadone reduction and so were maintained on PN. This is the first mention in this literature that PN might have a withdrawal syndrome severe enough not to be manageable by at least some addicts, and is only alluded to and not described.

Schmalstieg et al. (1975) also reported clinical experience with four patients withdrawing from heroin on PN. This study paralleled that reported above in dose--600 to 1200 mg day--and with favorable outcomes. "Speeding" and euphoria were observed in "some" of the patients when PN dose was high.

In summary, the clinical reports reviewed above indicate good patient acceptance of PN. The observations made

suggest that PN had a low toxic therapeutic ratio which while limiting its abuse potential also appears to limit its usefulness in withdrawing or maintaining high dose heroin addicts or high dose methadone maintenance patients. The side effects of hallucinations and dysphoria appear to be of a nature which, despite local bias, might in the long run not be tolerated well, and where local bias for PN did not exist, might not be tolerated at all. Efficacy cannot be discussed in relation to these studies because of a lack of experimental design, a lack of systematic recording of clinical events, and inadequate reporting. In particular these reports do not specify methods; it appears that if patients complained the complaints were noted but no systematic examinations were carried out and no instruments for doing so are mentioned in these reports.

EXPERIMENTAL STUDIES

The first experimental study of PN was reported in 1975 by Tennant et al. (1975b). Seventy-two heroin addicts were randomly assigned to a 21-day detoxification in which they received, under double blind conditions, either methadone 24 mg or PN 800 mg daily. Methadone retained patients in treatment longer than PN and suppressed opiate abstinence more than PN. Use of illicit drugs did not differ between methadone and PN groups. Follow-up interviews of 88 percent of the patients 1 month following detoxification disclosed no statistically significant differences in the two groups in terms of the number with an opiate free urinalysis. But five PN patients versus no methadone patients were drug free by urinalysis. The dose of PN may have been lower than the dose which would have been used under open conditions. In previous studies doses ranged from 600 to 1400 mg daily. Thus the difference in groups may have been a function of the low dose of PN employed.

In 1978 Kestenbaum et al. reported a double-blind study of 150 opiate dependent outpatients who were randomly assigned to PN, low dose methadone or diazepam as maintenance therapy for an 8-month period. The first month was devoted to stabilization followed by variable period of maintenance which could not exceed 6 months and then a variable period of detoxification which could not exceed 6 weeks (Kestenbaum et al. 1978). Dose of experimental medication, given twice a day, was titrated according to clinical need but could not exceed 36 mg of methdone

daily, 1200 mg PN daily, or 60 mg diazepam daily. Detoxification was achieved on a fixed schedule of two doses per day. For methadone, only one dose a day was active; the second methadone dose was a placebo.

Retention in treatment in the methadone group was significantly better than in the PN or diazepam groups. Only 15 patients completed the study. Although in absolute terms methadone patients were better represented in study completion (eight of 15), the differences were not statistically significant. Kestenbaum et al. commented that "there was no evidence of toxicity during maintenance on PN" but did report a seizure in a PN patient on 1000 mg daily. Kestenbaum et al. concluded, "With the doses employed, methadone has a greater capacity to retain patients in treatment, and PN is no more efficacious than active placebo i.e. diazepam." This assessment appears to be well supported by the findings in this study.

Woody et al. conducted a two-city study with essentially the same study design described above by Kastenbaum (Woody et al. 1981). Woody et al. concluded, "Our findings indicate that PN is a less satisfactory medication than methadone for maintenance treatment of opiate addiction. PN patients tended to drop out of treatment earlier, and even those who did remain in treatment one month or longer were more likely to terminate for a reason which indicated poor progress. They were also more likely to abuse heroin... a small number of PN patients dropped out due to signs and symptoms of CNS 'irritability'.... "Follow-up of patients in both centers at 6 months, however, disclosed no differences between groups. The Philadelphia group contacted study patients at 6 months and found that "approximately 22 percent of the patients interviewed at 6 months in each treatment group were drug free (by urine and interviews)."

The authors of this two-center study report that the findings of their study could have been influenced by a) selection procedures, e.g., patients in Philadelphia were admitted immediately to the study while in Los Angeles patients, for reasons not made clear, had to wait 5 to 10 days before being admitted to the study; b) local bias--in Philadelphia, a possible pro-methadone bias and in Los Angeles, a definite pro-PN bias; and finally c) access to other treatments--in Philadelphia patients could get treatment in accessible free methadone programs while in Los Angeles study patients did not have similar access.

Both of the centers involved in this study made reports to NIDA. Review of these reports does not alter the conclusions or alter significantly the data presented.

DISCUSSION

PN may be used as a detoxification agent and as a maintenance agent in treatment of opioid dependence. Therefore, I will separate these two uses in my discussion. At the outset we must remember that all of our data on PN have excluded patients with severe medical and psychiatric problems; that the twice-a-day or more frequent dose is compared to once-a-day methadone; and that subjects in studies were selected for having mild degree of dependence. We therefore have important observations on efficacy before reviewing the data acquired under limited test conditions.

PN as Detoxification Agent

Studies by Jasinski et al. (1977) and by Tennant et al. (1977) under double blind controlled conditions indicate that PN is a weak morphine-like agonist with a potency ratio of 50 to 60 mg of PN to 1 mg of morphine s.c. In addition Jasinski et al. reported, "Toxic effects limit the degree of morphine-like activity produced by single doses of propoxyphene napsylate, however, to that produced by 10 mg of morphine subcutaneously". There would appear to be little question that the toxic therapeutic ratio for use in detoxification is low, with daily doses of PN in excess of 1000 mg generating side effects of hallucination, seizure-like or frank seizure activity, and dysphoric states. While these effects limit the dependence-producing liability of PN, they also limit its therapeutic use to those opioid dependent persons with relatively mild habits. Use of PN as a sole detoxification agent for moderate or severe degrees of opioid dependence has not been investigated systematically. It appears highly unlikely that PN used alone would be efficacious in moderate or severe degrees of opioid dependence, but again we have no data. The practical question is whether PN used alone is efficacious for detoxification of persons with mild degrees of opioid dependence. The evidence of the controlled studies reviewed above is that PN in comparison to the current standard of methadone supported detoxification is not as efficacious in retaining patients in treatment and in suppressing opioid

withdrawal symptoms. In the studies reviewed neither PN nor methadone had efficacy in producing abstinence.

The question of degree of biologic dependence and its relevance to these studies is underscored in Tennant's study of PN versus placebo. Seven of 18 placebo patients had no withdrawal symptoms. If seven of every 18 patients involved in Tennant's previous work were similar, then the meaning of his observations is importantly changed and the efficacy of PN appears to be more remote.

PN as a Maintenance Agent

Given the fact that we have data on fewer than 100 patients who have been taking PN as a maintenance agent for as long as 6 to 10 months, the questions of efficacy cannot be answered adequately. The studies conducted in Philadelphia, New York, and Los Angeles indicate that PN is inferior to methadone in terms of treatment retention, but given the high dropout rates encountered in both PN and methadone groups in these studies, the efficacy of either agent has to be questioned. The condition of "being in a study" appears to account for the abnormally high dropout rate for methadone maintenance patients. The national data suggest that methadone maintenance usually retains 50 percent of patients for the first year of treatment. It would appear that those with mild degrees of opioid dependence would fare best on PN as a maintenance agent. The question of safety has not been answered for PN in long-term use.

CONCLUSION

The efficacy of PN as a detoxification agent or as a maintenance agent has not been established. It would appear to be useful for patients who are minimally dependent on opioid drugs, and are from communities with a strong antimethadone bias. In view of its low toxic therapeutic ratio and the necessity of twice-daily administration in comparison to methadone, further exploration of PN has a low priority. However, its concurrent use with methadone as an adjunct to detoxification should be explored further.

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CRITIQUE

William A. Hargreaves, Ph.D.

Dr. Senay presents a clear and balanced summary of the evidence on the issue of the effectiveness of propoxyphene napsylate (PN) in detoxification and maintenance treatments. In detoxification, PN is not as effective as methadone in maintaining patients in treatment or suppressing heroin use, even among persons thought to have relatively mild addiction to heroin (the only people on whom PN has been tested). In maintenance, trends are also seen for methadone to be superior to PN, but dropout rates have been so high that firm conclusions cannot be drawn.

I have no major quarrel with Dr. Senay's review of the individual studies. However, the most interesting study, because of its inclusion of an "active placebo" diazepam treatment group, was not available to me for review (Kestenbaum et al. 1978). It may be, as Dr. Senay implies, that after the significantly higher attrition in the PN and diazepam groups compared to the methadone group, no further interpretation of the results is possible.

The study by Woody et al. (1980a; 1980b; 1981) is similar to the Kestenbaum et al. study but did not include the diazepam control group. Two of the three Woody et al. papers are essentially duplicates. Altogether Woody et al. seemed to do a good job of making sense of their data, although the key urine test results are analyzed clumsily so that some of the power of the study is lost. This test did show that, for Ss who survived the first month, subsequent opiate abuse was higher in the PN group than in the methadone group. The authors do not examine whether their groups are still equivalent after attrition. Presumably both groups would be more likely to lose Ss who were abusing opiates heavily, with the higher attrition in the PN group leaving that group more selectively well functioning. But if it happened to have gone the other way, it would have compromised the interpretation of the later opiate abuse analysis.

Dr. Senay offers the conservative policy recommendation that the lack of evidence for the utility of PN makes further work with this compound a low priority. I agree

that it should probably be a low priority, but I think the research results we have at hand do not really address the policy issues one should be considering here. Suppose further work confirmed the present tentative conclusion that PN is less effective than methadone, and not more effective than diazepam. In the first place, diazepam is far from an inert compound, and is one of several palliative drugs used in "symptomatic" detoxification. We have no information, to my knowledge, about the effectiveness of "symptomatic" or drug free detoxification, except the nonexperimental finding that "evaluation only" patients have outcomes similar to those who receive brief detoxification treatment. There is also the fact that even in methadone supported detoxification very few patients report being abstinent a few months later. A small proportion of addicts reduce or even temporarily stop their daily use of heroin following brief detoxification, and these patients may in fact be experiencing some treatment benefit; the question has never been studied experimentally. It may also be that adjunctive medications used in this context contribute to subject retention and outcome. Thus PN may have a place here for patients to whom we would not want to give methadone, especially in communities in which methadone is acceptable only for a very narrow group of hardcore addicts, or where the demand for maintenance treatment exceeds the supply of treatment slots.

I think it is time to learn something about the effectiveness of the briefer treatments. Treatment resources are being curtailed, so there may now be an increasing number of addicts who would participate in treatment, but who are not in treatment due to a decreased availability of services. Such a shift could alter the relative cost effectiveness of the various treatment modalities. Methadone maintenance with treatment durations up to several years has so far seemed like the most effective treatment for addiction, on the basis of the evidence we have about outcomes of persons treated. But patients in briefer treatments sometimes show improvement. We just have no experimental evidence that such improvement is due to the treatment.

Suppose we knew that 3 months of a particular treatment had 10 percent of the effectiveness of 3 years on methadone maintenance, and the cost per patient-month was the same in the two treatments. If we had sufficient treatment funding to have every relevant addict in 3-year maintenance, to do so would give us the maximum impact on

recovery from addiction. With less funding, adding a treatment slot in the brief treatment would have the same impact as adding another maintenance slot, if the 10 percent effectiveness were applied to 10 times as many addicts. It would be ideal if we could base our allocation of treatment resources between extended maintenance and other treatments on information about the effect of these choices on the long-term community prevalence of addiction. We are currently lacking such information.

We need not only to shape existing modalities into their maximum effectiveness, but to assess in controlled studies the effectiveness of brief maintenance and the other even briefer modalities. Such work needs to recognize the heterogeneity among addicts in the treatments they will find acceptable. With regard to a drug like PN, one might ask whether the subgroup of addicts who will accept only PN detoxification, drug free detoxification, or no treatment, will differentially benefit from one of them. That is quite a different question from comparing methadone, PN, and diazepam in a group of heroin addicts who prefer methadone maintenance.

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DISCUSSION SUMMARY

James R. Cooper, M.D., Fred Altman, Ph.D., and Kim Keeley, M.D.

Dr. Cooper explained the Narcotic Addict Treatment Act (NATA) and the relevance of the Act to the review of propoxyphene napsylate (PN). NATA prohibits physicians from using narcotics to maintain/detoxify addicts dependent on narcotics other than those for which the Secretary of Health and Human Services has established treatment standards. The Secretary cannot develop standards for the use of a particular narcotic in opiate maintenance or detoxification treatment without the manufacturer submitting a New Drug Application (NDA) to the Federal Drug Administration for approval. The manufacturers of propoxyphene have not indicated a desire to submit an NDA. Thus, no standards can be developed and any physician who uses PN for this indication is in jeopardy of legal sanction. The purpose of the PN review/discussion was to determine if there is enough support from the group for developing either maintenance or detoxification standards for PN. Several years ago the National Institute on Drug Abuse (NIDA) funded a number of studies to investigate the safety and efficacy of PN as a maintenance agent. Eli Lilly and Company has investigated the safety and efficacy of PN as a detoxification agent. If an independent review of the data suggested that PN was effective for either indication, and the group concurred, NIDA would consider going to the manufacturer to discuss the possibilities of submitting an NDA for either indication.

The discussion covered topics such as: the lack of data to support the efficacy of PN as a detoxification or maintenance agent; its restricted applicability (e.g., PN is only appropriate for an unidentified subset of those who are mildly addicted to opiates); its low therapeutic index; its relative ineffectiveness when compared with methadone; and its greater acceptability in some communities because it is a less potent narcotic than methadone.

There was consensus that PN was not an effective maintenance agent and, with the exception of Dr. Senay, there was no support for the use of PN as a detoxification agent. Dr. Senay supported an availability of PN for detoxification of opiate addicts because he believes that there should be a narcotic less potent than methadone available for this purpose.

There was no support for either further research or for developing standards for PN for either indication.

CHAPTER 8. EFFICACY OF MAINTAINING OR DETOXIFYING OPIATE ADDICTS WITH THE DRUG OF ADDICTION VS. THE USE OF METHADONE AS A TREATMENT AGENT

James R. Cooper, M.D., Fred Altman, Ph.D., and Kim Keeley, M.D.

Unlike the other topics covered in these chapters, this topic was not initiated by a review paper because there was insufficient research literature. Nonetheless, NIDA staff are frequently asked to comment on the appropriateness and limitations of maintaining or detoxifying a person physically dependent on opiates other than heroin and methadone with the same drug to which the person is addicted. Thus, the participants' expert clinical opinions on this topic were sought.

Presently, a Federal statute (the Narcotic Addict Treatment Act P.L. 93-281) prohibits physicians from using narcotics to maintain/detoxify addicts dependent on narcotics other than those for which the Secretary of Health and Human Services (HHS) has established treatment standards.[1] Currently, methadone is the only narcotic for which standards have been established. Prior to the meeting the participants were informed that this topic would be discussed and were specifically asked to consider a number of matters related to such treatment, e.g., method for establishing the initial and stabilizing doses, frequency and duration of drug administration, treatment environment (hospital, outpatient, residential), etc. At the meeting it was explained that if there was general support for using the narcotic to which the person is addicted for either maintenance or detoxification NIDA could make such a recommendation and assist the Secretary in developing the standards.

The discussion covered a broad range of topics, such as the consequences of regulating drugs physicians may use, and problems of drug diversion. However, the conclusions

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[1]Standards are not required when narcotics are used to detoxify/maintain addicts for medical purposes other than their addiction, e.g., surgery. Likewise, standards are not required when narcotics are used to treat pain, irrespective of whether the patient is an addict.

reached were simple and explicit. All the participants agreed that methadone should be the only narcotic used for maintenance and detoxification from street addiction because of its ease of administration (oral), duration of action, and safety and efficacy.

It was recognized that some patients treated with narcotics for pain will become iatrogenically addicted. There was consensus that if such a patient no longer requires a narcotic for pain, that the patient should be gradually withdrawn from that narcotic to complete the original medical treatment. However, if the detoxification procedure is unsuccessful, everyone agreed that methadone should be the drug of choice for subsequent detoxification attempts.

There was no support for the Secretary of HHS establishing treatment standards for detoxification and/or maintenance treatment using the same narcotic to which the person is addicted. There was no support for research regarding this issue.

PART II

EFFECTS OF METHADONE ON OFFSPRING AND USERS

CHAPTER 1. DISPOSITION AND METABOLISM DURING THE PERINATAL PERIOD OF METHADONE AND OTHER DRUGS USED IN NARCOTIC ADDICTION TREATMENT

Hazel Szeto, M.D., Ph.D.

The most important question regarding any drug used during pregnancy is how much it affects the fetus. This concern is especially great in long-term maintenance of pregnant heroin dependents. In general, the more drug to which the fetus is exposed, the greater the adverse effects. Therefore the best drug for such therapy should be that resulting in the least fetal drug exposure.

At present, the only drug approved for maintenance use in pregnant women is methadone. However, no clinical or experimental evidence suggests that fetal drug exposure is least following this agent. Because related drugs such as acetylmethadol have not been used in pregnant women, no information is available on their disposition in the human maternal-fetal unit. Therefore animal models must be used to compare the dispositions of methadone and the other drugs.

This paper reviews current knowledge of the disposition of methadone and related drugs in the perinatal period, evaluates the approaches and techniques that have been used, and identifies areas for further investigation.

EFFECT OF PREGNANCY ON DRUG DISPOSITION

Methadone

Very little information is available on how pregnancy affects methadone disposition in methadone maintenance patients. Although plasma methadone concentrations at the time of delivery have been reported for a number of such patients (Blinick et al. 1975; Harper et al. 1977; Kreek 1979), comparison with nonpregnant maintenance patients has been difficult because dosages used have varied widely among patients. Even among pregnant patients, little if any correlation seems to exist between maternal plasma methadone concentration and daily methadone dose (see figure 1). Because of this large interindividual variation

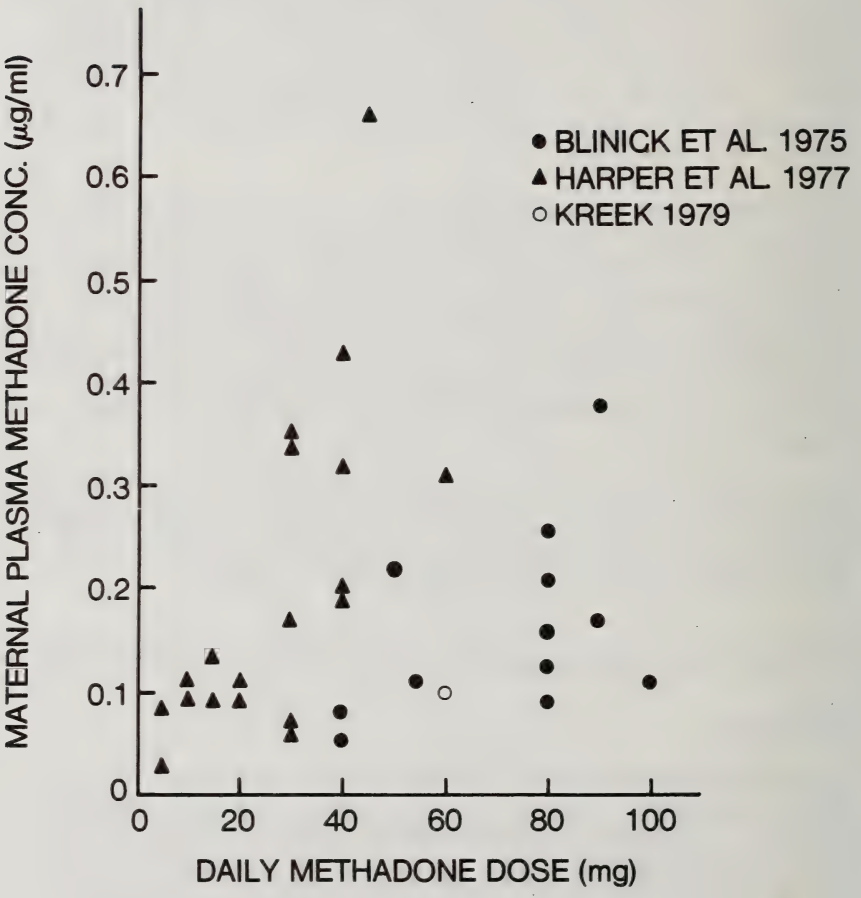


Figure 1. Relationship between maternal plasma methadone concentration at the time of delivery and daily methadone dose.

in steady-state plasma methadone concentration, the effect of pregnancy on methadone disposition must be determined by repeatedly studying the same patient.

Recent reports by Kreek (Kreek et al. 1974; Kreek 1979) on sequential studies in two patients throughout and shortly after pregnancy suggest that steady-state plasma methadone concentrations fall during pregnancy. The apparent lowering of plasma methadone concentration may be due to decreased plasma protein binding, increased methadone clearance, or both. Because no data are available on plasma protein binding of methadone in pregnant women, it is difficult to speculate whether methadone clearance is altered during pregnancy. Therefore studies on this topic are needed.

The results of a recent study on methadone binding in the pregnant ewe suggest that methadone binding decreases during pregnancy (Szeto et al. 1982a). The binding of methadone was higher shortly after delivery than in the third trimester. Although binding in control nonpregnant animals was not determined, this finding does suggest that the extent of protein binding would be important to determine in humans.

At present, little is known about the influence of pregnancy on the distribution and elimination of methadone. Animal studies have contributed little to our understanding. The distribution of radiolabeled drug has been studied in the pregnant rat and the pregnant rhesus monkey. Peters et al. (1972) found that methadone was similarly distributed to most tissues in pregnant and nonpregnant rats, except that the uterus contained three times as much methadone in the former. In monkeys, Davis and Fenimore (1978) found that ^{3}H-methadone content was higher in a variety of tissues in late rather than early gestation. In light of the tremendous interindividual variation observed in humans, more studies are needed before any conclusions can be made on the distribution of methadone in pregnancy. The major drawback of such tissue distribution studies is the large number of animals required to generate a concentration-time curve.

Related Drugs

No data now exist on the disposition of heroin, acetylmethadol, propoxyphene, and naltrexone in pregnant women. The disposition of morphine has been studied at the time

of delivery, but it is unclear how the effects of the physiologic state of pregnancy can be separated from those of the stress of labor and the concurrent use of other medications. A preliminary report by Man et al. (1980) states that the distribution of acetylmethadol is similar in pregnant and nonpregnant rats.

DRUG DISPOSITION IN THE MATERNAL-FETAL UNIT

Human Studies

The concentrations of methadone in maternal and cord plasma at the time of delivery have been determined in 30 patients in two major studies by Blinick et al. (1975) and Harper et al. (1977) and in one patient by Kreek (1979) (see figure 2). In all cases, methadone concentration was lower in cord plasma than in maternal plasma, with mean cord/maternal ratios of 0.57 in Blinick's study and 0.26 in Harper's study.

The lower concentration of methadone in cord than maternal plasma has been attributed to the extensive binding of methadone to maternal plasma proteins (Harper et al. 1977), different binding characteristics to fetal plasma proteins (Blinick et al. 1975), biotransformation of methadone by placental and fetal tissues (Blinick et al. 1975), and fetal urinary excretion of methadone (Harper et al. 1977). Unfortunately, further studies in humans have not contributed significantly to understanding the factor(s) determining the ratio of fetal/maternal concentrations. At present, there are no data on the binding of methadone in maternal or cord plasma. Both methadone and its metabolites have been detected in neonatal urine (Blinick et al. 1975; Harper et al. 1977; Kreek 1979), but it is unclear whether the extent of urinary excretion *in utero* is sufficient to account for the maternal/fetal concentration difference.

Animal Models

Studies using small laboratory animals have demonstrated only that methadone is distributed to the fetus after being administered to the mother. In order to understand the factor(s) determining the distribution of a drug between the mother and fetus, and to obtain quantitative data for comparing the various narcotic drugs, we need an

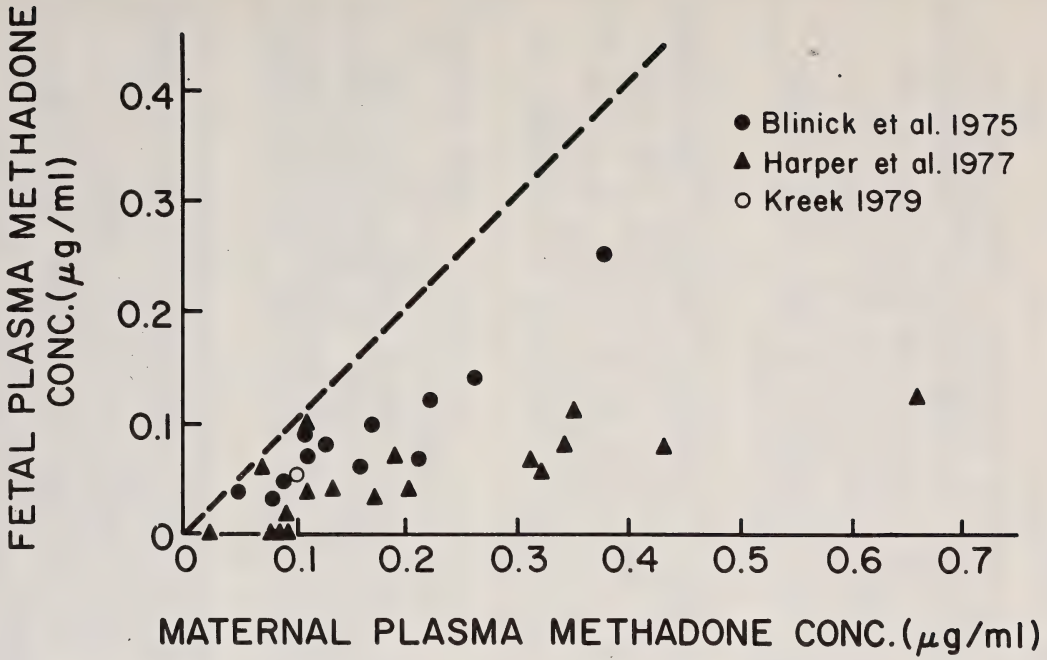


Figure 2. Maternal and cord plasma methadone concentrations in methadone maintenance patients.

animal model that allows us to investigate not only maternal and fetal plasma drug concentrations but also maternal and fetal plasma protein binding and fetal drug elimination. In the last few years, my colleagues and I have found the pregnant ewe to be the most suitable animal model for such studies.

We have developed surgical techniques allowing chronic indwelling catheters to be implanted in several maternal and fetal blood vessels, so that throughout the third trimester we can sample maternal and fetal blood at any time after drug administration in an unanesthetized, unrestrained animal (Szeto et al. 1978). Using such animals, we have studied the disposition of methadone in the maternal fetal unit and compared it with those of meperidine, morphine, and acetylmethadol.

Methadone is transferred to the fetus very rapidly after an intravenous dose to the mother. It can be demonstrated in the umbilical vein within 2 minutes after drug administration, and peak fetal arterial concentration occurs within 5 to 10 minutes (Szeto et al. 1981). Methadone is eliminated at similar rates in the fetus and in the mother; the mean halflife is 59 minutes in the former and 57 minutes in the latter.

Steady state is achieved in both mother and fetus following a 5-hour infusion of methadone to the mother at a constant rate of 5 μg/kg/min. Even at steady state, fetal plasma concentration remains lower than maternal plasma concentration (Szeto et al. 1981). In two separate studies, the ratios of fetal to maternal steady-state concentration were 0.15 (Szeto et al. 1981) and 0.18 (Szeto et al. 1982c) (see table 1).

Part of this difference can be attributed to the difference in maternal and fetal plasma protein binding of methadone. Mean maternal plasma binding was 76.2 + 1.3 percent in the third trimester (Szeto et al. 1982a); fetal binding was significantly lower than maternal binding early in the third trimester but increased rapidly toward the last 2 weeks of pregnancy (Szeto et al. 1982a) and approached maternal binding by the time of parturition. Such rapidly changing binding characteristics and the later interindividual variation even within the same gestational age group make interpretation of total drug distribution between mother and fetus quite meaningless.

Table 1. Fetal/maternal steady-state concentration

Drug	Fetal concentration / Maternal concentration (total)	Fetal concentration / Maternal concentration (free)	Reference
Methadone (n=5)	0.15 ± 0.02 (SE)	0.40 ± 0.04	Szeto et al. 1981
(n=7)	0.18 ± 0.03	0.42 ± 0.07	Szeto et al. 1982c
Meperidine (n=6)	0.30 ± 0.04	0.46 ± 0.06	Szeto et al. 1978
Morphine (n=7)	0.14 ± 0.01	0.14 ± 0.01	Szeto et al. 1982c
LAAM (n=4)	0.11 - 0.51	NA[1]	Szeto et al., unpublished data

[1]Not available.

However, even when the concentrations only of unbound methadone were compared, fetal steady-state concentration was lower than maternal concentration (see table 1). Therefore, binding alone cannot account for the concentration gradient at steady state.

Table 1 also compares the distributions of methadone, meperidine, morphine, and acetylmethadol in the pregnant ewe. For each, the concentration of unbound drug in the fetus is lower than that in the mother. Because the ratio of fetal to maternal steady-state concentration for unbound meperidine resembles that for methadone, the former would offer little advantage for chronic use in pregnancy. However, the ratio is three times smaller for morphine, suggesting that fetal exposure to morphine is less than that to methadone. The data for acetylmethadol are very limited at present. In two of the four animals, this drug was not detectable in fetal plasma, so that the ratios were less than 0.1. Protein binding data for acetylmethadol are not yet available.

The pregnant ewe model has therefore allowed us to obtain quantitative data for comparing the distributions of several narcotic drugs in the maternal-fetal unit.

PHARMACOKINETIC ANALYSIS OF THE MATERNAL-FETAL UNIT

In the past 2 years, my colleagues and I have tried to determine the factor(s) governing the different distributions of these narcotic drugs between the mother and fetus. Figure 3 represents the simplest model of the maternal-fetal unit; mother and fetus each are represented as a single compartment. In this model, there is bidirectional transfer of drug between the two compartments, and elimination of drug from each. The amount of drug to which the fetus is exposed is therefore determined by the clearance of drug from mother to fetus and the clearance of drug out of the fetal compartment, through both the placenta and nonplacental tissues such as the liver and kidneys.

The extent of fetal exposure to drugs therefore depends on these clearance terms. To determine these clearance terms quantitatively, drug must be administered into both compartments and the resultant concentrations measured in each. The pregnant ewe model is ideally suited for such purposes.

Four mass-balance equations can be written describing the concentrations of drug in the two compartments following drug infusion to the mother and fetus at steady state. Thus, there are four equations and four unknown clearance terms. These equations can be solved simultaneously, and the four clearance terms calculated. The derivations and solutions of these equations are presented in Appendix 1.

The solutions show that when a drug is administered to the mother, the ratio of fetal to maternal steady-state drug concentration is determined by the following relationship:

$$\frac{\bar{C}_F}{\bar{C}_M} = \frac{CL_{MF}}{CL_{FM} + CL_{FO}}$$

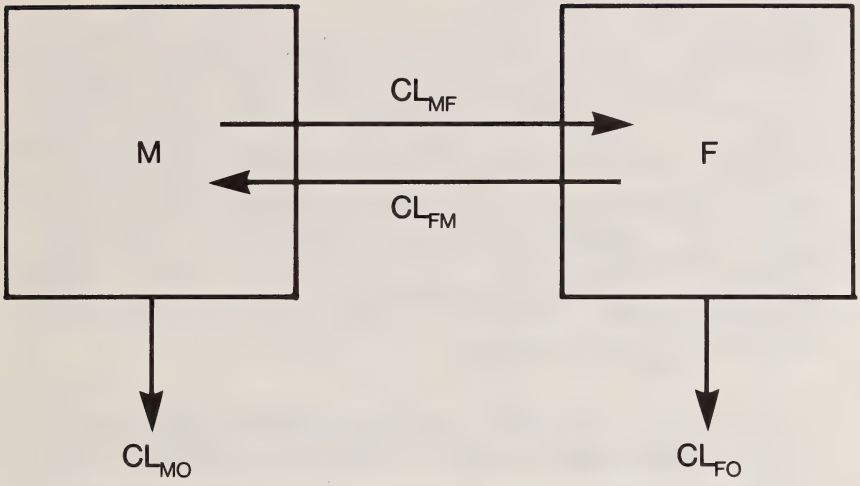


Figure 3. A two-compartment model describing the disposition of a drug in the mother and fetus, where M represents the maternal compartment and F represents the fetal compartment; CL_{MF} and CL_{FM} are the respective placental drug clearances from the maternal to the fetal compartment and from the fetal to the maternal compartment; and CL_{MO} and CL_{FO} are the respective nonplacental clearances from the maternal and fetal compartments.

Therefore, if the drug is not eliminated by the fetus (i.e., $CL_{FO} = 0$), the maternal and fetal compartments will come into equilibrium at steady state, and fetal and maternal drug concentrations will always be equal. In this case, the transplacental clearances will be equal ($CL_{MF} = CL_{FM}$). This relationship, of course, applies only to the concentrations of unbound drug in the two compartments.

However, as long as fetal clearance is greater than zero, fetal concentration will always be less than maternal concentration. In this situation, there is a steady state but not an equilibrium. Surprisingly, the permeability of the placenta does not influence the distribution of a drug

between the mother and fetus at steady state; it determines only the time needed to approach maternal-fetal equilibrium (Riggs 1963).

The data on the distributions of the above four drugs at steady state indicate that all must be eliminated by the fetus. Data are now available on the fetal and placental clearances of methadone and morphine in the pregnant ewe (Szeto et al. 1982c) (see table 2). The clearance of morphine from mother to fetus is signficantly slower than that of methadone; this difference can be accounted for by a much lower apparent partition coefficient of morphine than of methadone (Kaufman et al. 1975). Although fetal clearance of morphine is somewhat lower than that of methadone, the slower clearance of morphine across the placenta permits fetal exposure to be lower.

Table 2. Placental and nonplacental clearances of methadone and morphine in the maternal-fetal unit

Drug	CL_{MF} (ml/min)	$CL_{FM}+CL_{FO}$ (ml/min)	CL_{FO} (ml/min)
Methadone (n=7)	390.3 ± 92.8	885.0 ± 154.1	381.0 ± 89.1
Morphine (n=7)	24.9 ± 3.0	184.0 ± 17.5	115.6 ± 15.3

At present, clearance data are available only for methadone or morphine. More extensive information would be most helpful in choosing a drug for maintenance therapy during pregnancy. The ideal drug would have a very low placental clearance and a very high fetal clearance.

Fetal Clearance of Methadone

Fetal clearance of methadone may include renal excretion and biotransformation to metabolites. To use the pregnant ewe model to determine renal clearance of methadone *in utero*, we placed catheters directly into the bladder of the fetus (Szeto et al. 1981). Figure 4 shows the cumulative excretion of methadone into fetal urine. The renal clearance of methadone was calculated to be 5 to 15 ml/min, which is only a very small fraction of total fetal clearance. In the fetal lamb as in the adult human,

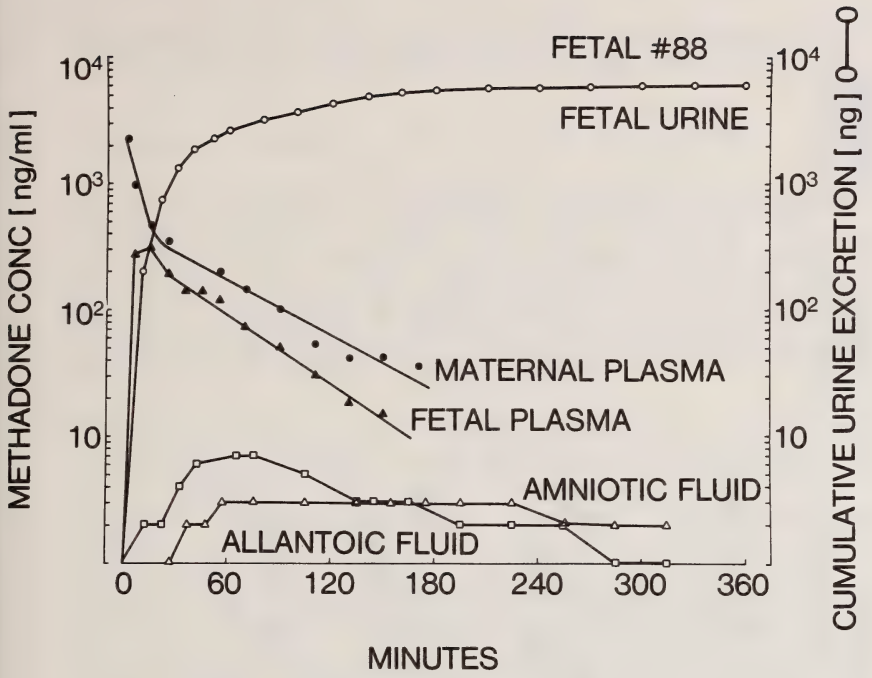


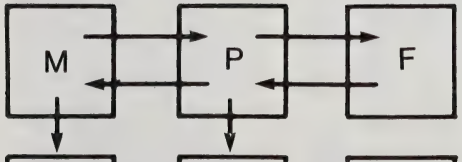
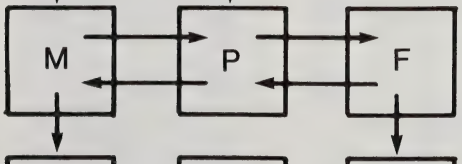
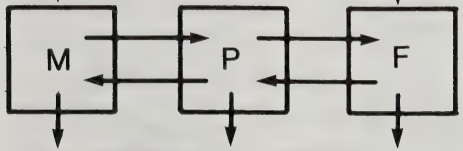
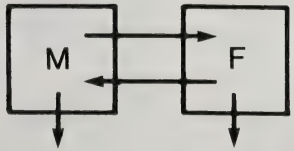
Figure 4. Cumulative excretion of methadone in fetal urine (o----o) following an intravenous bolus of methadone to the mother.

biotransformation is most likely the predominant pathway for eliminating methadone.

Placental Drug Elimination

The previous section showed that fetal drug elimination will result in a lower fetal than maternal concentration. What about placental drug elimination? Some investigators have criticized the two-compartment model as being too simple and have suggested using a three-compartment model including a "placenta." Three such models, illustrated on page 258, can be proposed for the maternal-placental-fetal unit.

However, such models pose some problems. First, the placenta does not fulfill the criteria of a separate compartment, for it is composed of maternal and fetal blood vessels in close apposition. Second, adding a "placental compartment" makes it impossible to verify the model, for one cannot infuse into the placenta or sample "placental fluid." Therefore, the unknown clearances outnumber the equations that can be written. Finally, placental drug

MODEL	STEADY-STATE CONCENTRATION		NUMBER OF CLEARANCES TO BE CALCULATED	NUMBER OF INDEPENDENT EVALUATIONS THAT CAN BE WRITTEN
	INFUSION TO M	INFUSION TO F		
	$\bar{c}_M > \bar{c}_P = \bar{c}_F$ $(\bar{c}_M > \bar{c}_F)$	$\bar{c}_F > \bar{c}_P > \bar{c}_M$ $(\bar{c}_F > \bar{c}_M)$	6	4
	$\bar{c}_M = \bar{c}_P > \bar{c}_F$ $(\bar{c}_M > \bar{c}_F)$	$\bar{c}_F = \bar{c}_P > \bar{c}_M$ $(\bar{c}_F > \bar{c}_M)$	6	4
	$\bar{c}_M > \bar{c}_P > \bar{c}_F$ $(\bar{c}_M > \bar{c}_F)$	$\bar{c}_F > \bar{c}_P > \bar{c}_M$ $(\bar{c}_F > \bar{c}_M)$	7	4
	$\bar{c}_M > \bar{c}_F$	$\bar{c}_F > \bar{c}_M$	4	4

elimination would not alter the relationship between maternal and fetal drug concentrations at steady state.

SPECULATIONS

The ultimate question is whether the extent of fetal exposure to methadone differs from that to heroin. At present, no data are available on the disposition of heroin in the maternal-fetal unit. However, the data on placental and fetal clearances of methadone and morphine allow some interesting speculations regarding the possible disposition of heroin between mother and fetus.

Because heroin is highly lipid soluble, it can be expected to be rapidly cleared across the placenta from mother to fetus. However, heroin also is rapidly hydrolyzed to 6-monoacetylmorphine (6-AM) in blood and then to 6-AM and morphine in most tissues, including those of the human neonate (Way et al. 1965). The overall disposition of heroin in the maternal-fetal unit therefore depends on the rates and extents of hydrolysis in mother and fetus. 6-AM is relatively lipid soluble and can be expected to be cleared rapidly from fetus to mother. However, 6-AM may be rapidly hydrolyzed to morphine, the fetal-to-maternal clearance of which is much slower. The rapid influx of heroin or 6-AM into, and the much slower efflux of morphine from, the fetus would cause the fetus to act as a sink for morphine.

Studies on the disposition of heroin and its metabolites in the maternal-fetal unit may help us understand why neonates of methadone dependent mothers appear to do better than those of heroin dependent mothers.

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APPENDIX 1

THEORETICAL CONSIDERATIONS

The basic assumptions made in deriving the equations for transplacental and nonplacental clearances are as follows:

1. The distribution of the drug between the mother and the fetus and the nonplacental elimination of the drug from the mother and the fetus are all first-order kinetic processes.

2. At steady state, the distribution of the drug between mother and fetus can be represented by the two-compartment open model shown in figure 3.

When a drug is administered to the mother at a constant infusion rate, J, a steady state will be attained in the mother when the rate of infusion equals the rate of elimination from the maternal compartment by all routes. Similarly, a steady state will be attained in the fetus when the rate of drug input into the fetal compartment equals the rate of elimination by all routes from the fetal compartment. The following rate equations describe the changes in amount of drug with time in the maternal and fetal compartments at steady state:

$$\frac{dX_M}{dt} = J + (k_{FM}V_F)\bar{c}_F - (k_{MF}V_M + k_{MO}V_M)\bar{c}_M = 0 \quad (1)$$

$$\frac{dX_F}{dt} = -(k_{FM}V_F + k_{FO}V_F)\bar{c}_F + (k_{MF}V_M)\bar{c}_M = 0 \quad (2)$$

where X_M and X_F are the respective amounts of drug in the mother and fetus, $\bar{c}_M$ and $\bar{c}_F$ are the respective steady-state drug concentrations in the mother and fetus, and V_M and V_F are the respective volumes of distribution of the maternal and fetal compartments.

Equations (1) and (2), which were expressed in amounts, may be expressed in terms of drug concentrations in the maternal and fetal compartments:

$$\frac{dc_M}{dt} = \frac{J}{V_M} + \frac{k_{FM}V_F}{V_M}\bar{c}_F - (k_{MF} + k_{MO})\bar{c}_M = 0 \qquad (3)$$

$$\frac{dc_F}{dt} = -(k_{FM} + k_{FO})\bar{c}_F + \frac{k_{MF}V_M}{V_F}\bar{c}_M' = 0 \qquad (4)$$

Similarly, when a drug is administered to the fetus at a constant rate, J', the maternal and fetal drug concentrations at steady state can be described as follows:

$$\frac{dc_F}{dt} = \frac{J'}{V_F} + \frac{k_{MF}V_M}{V_F}\bar{c}_M' - (k_{FM} + k_{FO})\bar{c}_F' = 0 \qquad (5)$$

$$\frac{dc_M}{dt} = \frac{k_{FM}V_F}{V_M}\bar{c}_F' - (k_{MF} + k_{MO})\bar{c}_M' = 0 \qquad (6)$$

where $\bar{c}_M'$ and $\bar{c}_F'$ are the respective steady-state concentrations in the mother and fetus during drug infusion into the fetus.

Substituting equation (6) into equation (3), we obtain an expression for the total clearance of drug from the maternal compartment (CL_{MM}):

$$CL_{MM} = (k_{MF} + k_{MO})V_M = \frac{J}{\bar{c}_M - \bar{c}_F\left(\frac{\bar{c}_M'}{\bar{c}_F'}\right)} \qquad (7)$$

Similarly, by substituting equation (4) into equation (5), we obtain an expression for the total clearance of drug from the fetal compartment (CL_{FF}):

$$CL_{FF} = (k_{FM} + k_{FO})V_F = \frac{J'}{\bar{c}_F' - \bar{c}_M' \left(\frac{\bar{c}_F'}{\bar{c}_M'}\right)} \quad (8)$$

Equations (4) and (6) then allow the calculation of the clearance of drug from the maternal to the fetal compartment (CL_{MF}):

$$CL_{MF} = k_{MF}V_M = CL_{FF} \frac{\bar{c}_F}{\bar{c}_M} \quad (9)$$

and the clearance of drug from the fetal to the maternal compartment (CL_{FM}):

$$CL_{FM} = k_{FM}V_F = CL_{MM} \frac{\bar{c}_M'}{\bar{c}_F'} \quad (10)$$

Furthermore, the contribution of nonplacental mechanisms to the clearances of drug from the maternal and fetal compartments can be determined as follows:

$$CL_{MO} = k_{MO}V_M = CL_{MM} - CL_{MF} \quad (11)$$

$$CL_{FO} = K_{FO}V_F = CL_{FF} - CL_{FM} \quad (12)$$

The above equations therefore allow the placental and nonplacental drug clearances from the maternal and fetal compartments to be determined.

CRITIQUE

Donald Perrier, Ph.D.

Quantitation of the processes involved in the placental transfer of and fetal exposure to drugs has received very little attention in the literature. The majority of studies have been concerned with a comparison of total blood, plasma, or serum concentrations of a given drug in the mother and fetus following administration to the mother, while others have looked at relative tissue levels. One of the first attempts to quantitatively describe placental drug transfer was a theoretical paper by Levy and Hayton (1973). About the same time, Kauffman et al. (1973) compared the time course and serum concentrations of penicillin G following the infusion of this antibiotic into both the mother and fetus. However, the studies of Dr. Szeto are the first to use a double infusion technique with a rigorous pharmacokinetic analysis of the resulting data to generate quantitative information on placental transfer of drugs and on the ability of the fetus to eliminate drugs.

Clearance Determination in Maternal-Fetal Model

While the placental transfer of drugs and their distribution and elimination characteristics in the mother and fetus are complex, a relatively simple pharmacokinetic model, as depicted in figure 1, can be used to describe these processes (Szeto et al. 1982). Assuming zero-order infusion of drug into the mother, the following differential or rate equations can be written for serum drug concentrations in the mother and fetus, C_m and C_f:

$$V_m \frac{dC_m}{dt} = k_{om} + Cl_{fm} C_f - (Cl_{mo} + Cl_{mf}) C_m , \quad (1)$$

and

$$V_f \frac{dC_f}{dt} = Cl_{mf} C_m - (Cl_{fm} + Cl_{fo}) C_f , \quad (2)$$

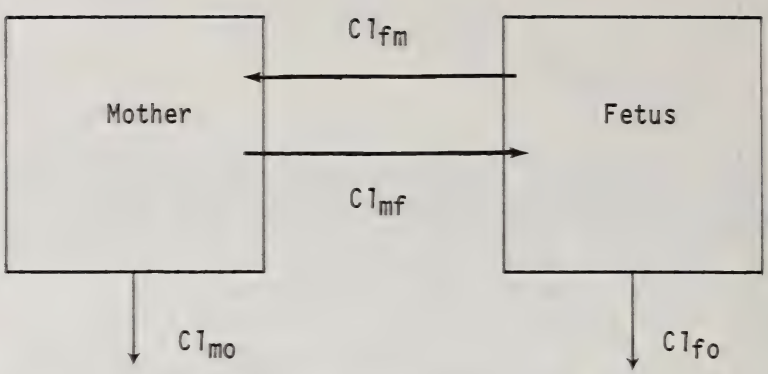

Figure 1. Pharmacokinetic model of the maternal-fetal unit.

respectively. In these relationships, k_{om} is the zero-order rate for drug infusion into the mother, V_m and V_f are the maternal and fetal volumes of distribution, Cl_{mo} and Cl_{fo} are the sums of maternal and fetal clearances of drug by metabolism and excretion, and Cl_{mf} and Cl_{fm} are the maternal to fetal and fetal to maternal clearances. If drug is infused into the fetus rather than the mother, the following relationships would result:

$$V_m \frac{dC'_m}{dt} = Cl_{fm} C'_f - (Cl_{mo} + Cl_{mf}) C'_m, \qquad (3)$$

and

$$V_f \frac{dC'_f}{dt} = k_{of} + Cl_{mf} C'_m - (Cl_{fm} + Cl_{fo}) C'_f, \qquad (4)$$

where k_{of} is the zero-order rate for drug infusion into the fetus. C'_m and C'_f are the serum concentrations of drug in the mother and fetus resulting from the administration of drug to the fetus.

Infusion of drug to steady state in the mother and fetus permits a solution for all of the clearance values defined above. Under steady-state conditions, equations (1) to (4) equal zero, and all concentrations will be steady-state concentrations. Solving the equations resulting from setting (1) and (3) equal to zero for Cl_{fm}, and setting the resulting expressions equal to each other yields:

$$\frac{Cl_m C_m - k_{om}}{C_f} = \frac{Cl_m C'_m}{C'_f} , \tag{5}$$

where Cl_m, the total maternal clearance, is given by:

$$Cl_m = Cl_{mo} + Cl_{mf} . \tag{6}$$

Equation (5) can be solved for Cl_m to give

$$Cl_m = \frac{k_{om}}{C_m - C_f (C'_m/C'_f)} . \tag{7}$$

Using the same approach, equations (2) and (4) can be employed to obtain an expression for Cl_f, the total fetal clearance, that is

$$Cl_f = \frac{k_{of}}{C'_f - C'_m (C_f/C_m)} , \tag{8}$$

where

$$Cl_f = Cl_{fo} + Cl_{fm} . \tag{9}$$

Recognizing that $Cl_{fm} + Cl_{fo}$ in equation (2) equals Cl_f, and that $Cl_{mo} + Cl_{mf}$ in equation (3) equals Cl_m permits these equations, at steady state, to be solved for Cl_{mf} and Cl_{fm}; respectively, the resulting expressions are:

$$Cl_{mf} = Cl_f \frac{C_f}{C_m} \tag{10}$$

and

$$Cl_{fm} = Cl_m \frac{C'_m}{C'_f} . \tag{11}$$

Equations (6) and (9) can be readily solved for Cl_{mo} and Cl_{fo} to give:

$$Cl_{mo} = Cl_m - Cl_{mf} \tag{12}$$

and

$$Cl_{fo} = Cl_f - Cl_{fm} . \tag{13}$$

Therefore the measurement of the steady-state serum concentrations of a drug following the infusion of drug to steady state in both the mother and fetus enables the determination of all clearance terms in the maternal-fetal model (figure 1) using equations (7), (8), (10), (11), (12), and (13). All of these equations have been previously derived and used by Szeto et al. (in press) to describe morphine and methadone disposition. It should be emphasized that the determination of all six clearance terms requires that the drug be infused to both the mother and fetus.

Factors Affecting Clearance

The clearance (Cl) of a drug, regardless of whether it pertains to an excretion process (e.g., metabolic and

renal) or a maternal-fetal transfer process, can be shown to be dependent upon the blood flow associated with the process of interest, Q, the binding of drug to serum protein, i.e., the free fraction , and the intrinsic clearance of unbound drug, Cl_i, by the relationship (Wilkinson and Shand 1975)

$$Cl = \frac{Q \ \alpha \ Cl_i}{Q + \alpha \ Cl_i} \tag{14}$$

For internal consistency, serum flow should be used in equation (14) rather than blood flow, if the clearances and binding characteristics are determined based on the serum concentrations of the drug. Conversely, if blood flow is to be used, the clearance and binding parameters should be determined in blood. The relationship between blood and serum flows and clearances is discussed elsewhere (Lee et al. 1980).

There are two limiting cases of equation (14). For a drug with a very low intrinsic clearance, that is, Cl_i is much less than Q, equation (14) simplifies to

$$Cl = \alpha \, Cl_i \cdot \tag{15}$$

Therefore, the clearance of such drugs is independent of blood flow, but is directly dependent upon the serum binding properties and inherent or intrinsic ability of an organ or system to clear a given drug from the serum. At the other extreme, that is, where the intrinsic clearance of a drug is much greater than blood flow, equation (14) reduces to

$$Cl = Q \cdot \tag{16}$$

Under this condition, clearance becomes independent of the binding and intrinsic clearance characteristics of drug, but should change in proportion to any change in flow to the organ or system responsible for its clearance from the serum. The relative effect of flow, binding, and intrinsic clearance on the maternal fetal clearance is illustrated in tables 1 and 2 for methadone and morphine.

Table 1. Placental clearance characteristics of methadone[1]

Q_{mu}[2]	Cl_{mf}	α_m	Cl_{imf}	$\alpha_m Cl_{imf}$	Cl_{mo}	Cl_m	f_f
457(30)[3]	96(73)	0.25(29)	486	122	1838(36)	1938(37)	0.05(40)
Q_{fu}[2]	Cl_{fm}	α_f	Cl_{ifm}	$\alpha_f Cl_{ifm}$	Cl_{fo}	Cl_f	f_m
477(29)	298(59)	0.61(38)	1302	794	210(63)	508(53)	0.57(22)

[1] All clearance and flow values are in units of ml/min, Q_{mu} = uterine blood flow, Q_{fu} = umbilical blood flow, α_m = fraction unbound in mother, α_f = fraction unbound in fetus, Cl_{imf} = intrinsic uterine clearance, Cl_{ifm} = intrinsic umbilical clearance, f_f = fraction cleared by uterus, f_m = fraction cleared into mother. All binding and clearance data obtained from Szeto et al. (1982).

[2] Szeto, personal communication. Obtained at steady-state methadone concentrations.

[3] Numbers in parentheses are coefficients of variability.

Table 2. Placental clearance characteristics of morphine[1]

Q^2_{mu}	Cl_{mf}	α_m	Cl_{imf}	$\alpha_m Cl_{imf}$	Cl_{mo}	Cl_m	f_f
465(47)[3]	25(32)	>0.95	26	26	2797(23)	2821(23)	0.01(36)
Q^2_{fu}	Cl_{fm}	α_f	Cl_{ifm}	$\alpha_f Cl_{ifm}$	Cl_{fo}	Cl_f	f_m
466(25)	58(32)	>0.95	66	66	126(32)	184(25)	0.33(32)

[1] See footnote to table 1 for definition of parameters. All binding and clearance data obtained from Szeto et al. (1982).

[2] Szeto, Personal communication. Obtained under control conditions.

[3] Numbers in parentheses are coefficients of variability.

The intrinsic clearance of methadone from the mother to fetus, αCl_{imf}, is about 27 percent of uterine blood flow (table 1). Consequently, neither limiting case of equation (14) would apply and changes in serum protein binding, uterine blood flow, and intrinsic clearance would be expected to influence maternal to fetal clearance with binding and intrinsic clearance changes having the greatest effect. With regard to total maternal clearance, only about 5 percent is maternal-fetal clearance. Therefore the primary mechanism of methadone clearance in the mother is via the normal pathways of elimination, namely, hepatic and renal. Clearance by these latter pathways is significantly lower in the fetus relative to the mother, 210 versus 1838 ml/min. Fetal to maternal clearance is the predominant mechanism for removal of methadone from the fetus, accounting for about 57 percent of the total fetal clearance. Changes in umbilical flow, and intrinsic fetal to maternal clearance, should have a comparable effect on fetal to maternal clearance. Fetal plasma protein binding is considerably lower when compared to the mother, probably as a result of lower protein concentrations in the fetus.

Trends similar to those seen with methadone are seen with morphine. However, with morphine, changes in the maternal/fetal and fetal/maternal intrinsic clearances would have the greatest impact on both Cl_{mf} and Cl_{fm}.

Assessment of Fetal Exposure

Of importance in placental transfer studies is the assessment of the degree of fetal exposure to a drug which is being administered to the mother. One method to assess exposure would be to compare the total area under the serum concentration of unbound drug versus time curve in the fetus (AUC_f) to the total area under the serum concentration of unbound drug versus time curve in the mother (AUC_m) following administration of drug to the mother. Equations can be derived for maternal and fetal serum concentrations of drug by solving equations (1) and (2) for C_m and C_f. Integration of the resulting equations for maternal and fetal concentrations during and after cessation of infusion will yield expressions for the total areas under the respective concentration time curves. Defining relative exposure (RE) as the ratio of the fetal to the maternal areas yields

$$RE = \frac{AUC_f}{AUC_m} = \frac{Cl'_{mf}}{Cl'_{fm} + Cl'_{fo}} = \frac{Cl'_{mf}}{Cl'_f} \quad (17)$$

In equation (17), Cl'_{mf}, Cl'_{fm}, Cl'_{fo} and Cl'_f are the clearances of unbound drug (e.g., $Cl'_{mf} = Cl_{mf}/\alpha_m$). It can be demonstrated that if the drug being administered to the mother is infused to steady state, RE is also equal to the ratio of unbound fetal to maternal concentrations at steady state.

Based on equation (17) and the data of Szeto et al. (1982), the relative exposure of the fetus to methadone and morphine was estimated (mean ± SD) to be 0.43 ± 0.19 and 0.13 ± 0.03. The validity of the fetal to maternal area or steady-state concentration ratios as an index of fetal exposure requires that the drug exhibits similar binding characteristics to maternal and fetal tissues. If the volume of distribution on a per kg basis is similar for the mother and fetus, when both are calculated using unbound serum concentrations, this may suggest that the binding characteristics of a drug are similar in the mother and fetus. The influence of binding characteristics on volume of distribution (V) is illustrated by the following equation (Oie and Tozer 1979):

$$V = 7.2 + 7.8\,\alpha + \frac{V_t}{\alpha_t}\,\alpha \quad (18)$$

where α is as defined previously, V_t is physiologic volume minus the volume of the extracellular fluid space, and α_t is the fraction free or unbound in V_t. The value of V generated would be in liters/70 kg. Since V equals αV_f where V_f is the volume of distribution based on the concentration of unbound drug in the serum, equation (18) can be written in terms of V_f, that is:

$$V_f = \frac{7.2}{\alpha} + 7.8 + \frac{V_t}{\alpha_t} \quad (19)$$

Division of both sides of equation (19) by 70 kg will yield an expression for V_f in units of L/kg. The resulting relationship for V_f would be

$$V_f = \frac{0.10}{\alpha} + 0.11 + \frac{0.014}{\alpha_t} V_t . \quad (20)$$

Therefore, changes in the relative degree of binding to maternal versus fetal tissue would alter volume of distribution. Most drugs of abuse are weak bases which tend to have relatively large volumes of distribution as a result of a high degree of tissue binding, that is, a small value of α_t. Consequently, small changes in binding may be anticipated to produce significant changes in volume of distribution for these drugs. Differences between the mother and fetus in the extent of tissue binding, and hence volume of distribution, should therefore be considered when interpreting relative exposure as determined by area or steady-state serum concentration ratios.

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CRITIQUE

Leon I. Mann, M.D.

INTRODUCTION

Controversy surrounding the question of what is the appropriate drug for use in detoxification and management of heroin addiction during pregnancy has remained unresolved. It is clear that heroin addiction and the resulting poor pregnancy outcome is a major health care problem. What is not clear is whether management with alternative drugs results in a significant improvement in both short-term outcome as measured by perinatal morbidity and mortality, and long-term outcome as measured in terms of infant morbidity and the development of subnormal motor and mental functioning.

Clinical reports of drug addiction or methadone maintenance during pregnancy have dealt primarily with observations of pregnancy outcome variables from a relatively limited series of patients (Blinick et al. 1973; Rahbar, 1975; Rothstein and Gould 1974; Kreek et al. 1974). Human maternal/fetal transport characteristics for these drugs have been described by analyzing simultaneous determined samples of maternal serum, cord blood, and amniotic fluid samples obtained most often at the time of delivery (Blinick et al. 1975; Harper et al. 1977; Kreek 1979). The interpretation of both types of clinical observations is compounded and complicated by the multivariant analysis required. Factors such as lack of prenatal care, other drug abuse, alcoholism, schizophrenia, and malnutrition have complicated or rendered uninterpretable the analysis of most clinical reports on the topic. An example is the acknowledged higher incidence of low-birth-weight/small-for-gestational-age newborns associated with drug addiction or methadone maintenance in pregnancy. The absence of adequate prenatal care and nutrition counseling, the presence of pregnancy-induced hypertension, cigarette smoking, alcohol abuse, or malnutrition may, by themselves, be associated with a higher incidence of low-birth-weight/small-for-gestational-age newborns.

Few studies have been reported that have controlled for these factors in a methadone maintenance group. When adequate pre- and perinatal care is provided to methadone maintenance patients, it appears that the birth weight of

the newborns is minimally affected, or not affected at all (Strauss et al. 1974). In fact, the suggestion has been presented that newborns of patients maintained on methadone during pregnancy who are of low birth weight, and average for gestational age, show evidence of an acceleration of lung maturity when compared to a nondrug group of newborns of similar low birth weight/average for gestational age (Gluck and Kulovich 1973). This is translated clinically into a lower incidence and severity of respiratory distress syndrome and hyperbilirubinemia. It would seem to this reviewer that the appropriate study that needs to be conducted to answer many of these questions should require that the multivariables be reduced to the single variant of drug maintenance.

The clinical studies that are reported on the transport of narcotics, methadone in particular, from mother to fetus clearly indicate significant maternal/fetal transport, fetal elimination by placenta and nonplacental organs, particularly the kidneys (usually reported as amniotic fluid or neonatal urine concentrations), and newborn withdrawal observations consistent with fetal uptake and disposition of the drug. Clearly, the observations are a rough estimate of transport and disposition and would not fit anyone's definition of pharmacologically accurate data. The observation of methadone within the amniotic fluid as early as 14-18 weeks is interesting but not unexpected (Blinick et al. 1974). Fetal drug exposure throughout gestation could be soundly hypothesized. Pooled fetal cord blood or a maternal serum drawn at the time of delivery represents a step toward understanding maternal/fetal transport but falls way short of elucidating the kinetics of the mechanism. A slight improvement in the analysis of such data would be to obtain samples separately from the umbilical vein and umbilical artery rather than pooling the cord blood, and to report and consider in the analysis the acid base status of the mother and fetus and amount of protein binding when such samples are drawn. It is unlikely, however, that future research in the human will be contemplated, much less approved by human research committees, because of the substantial risks to mother and fetus under such investigative conditions. Chronic catheterization of the human mother and fetus is not possible because of the substantial risk of infection, morbidity, and mortality.

The experimental animal model, therefore, remains the main source of investigation for the answer to the questions

relating to disposition, uptake, metabolism, and elimination of these drugs. The choice of animal preparation assumes major importance in order to fulfill the main objective of the basic science experimentation, which must be to obtain data under steady-state conditions. The subhuman primate monkey or baboon model would be ideal and closest to the human, but is unfortunately difficult to prepare, expensive, and does not lend itself to chronic preparation where observations can be obtained under steady-state conditions. While further removed from the human than the monkey, the pregnant sheep preparation has several advantages to studies of this type (Mann et al. 1974). The fetus and mother can be prepared with catheters, flow probes, EEG electrodes, etc., early in the last third of gestation (term 145 days), recover from surgery within 48 hours, and be maintained successfully at least 80 percent of the time through delivery at term when the newborn lamb usually rights itself and walks away from its mother. Fetal blood volume is adequate for chronic sampling in order to determine biochemical, acid base, and drug levels which can then be correlated with the other physiologic or functional endpoints being measured. Of major significance is the large body of information that may be researched and applied to the proposed experimentation. The animals are docile, cooperative, and easy to work with. Much of our understanding of normal and abnormal in-utero development has been obtained from this preparation. It was, therefore, my pleasure to welcome Dr. Hazel Szeto to our laboratory some 7 years ago to learn the acute and chronic sheep model so that she would be able to apply her pharmacologic knowledge to the questions of disposition and metabolism of narcotics. Much of what we now know regarding this issue has come from the extensive work that she has performed over the past 6 to 7 years. Collaboration with her and other basic scientists has been beneficial and productive toward the cause of basic science in general, but particularly toward understanding better a most difficult clinical problem. Specific comments in response to Dr. Szeto's review follow.

METHADONE DISPOSITION IN PREGNANCY

The effect of pregnancy on methadone disposition in methadone maintenance patients remains unanswered. Dr. Szeto's figure, where maternal plasma concentration is correlated to the daily maintenance dose, clearly demonstrates the problem. The variation in maternal plasma concentration

at various daily maintenance doses is obviously too wide for interpretation. Whether this could be improved upon by controlling for blood sampling according to a standard time of day, period following ingestion, length of drug maintenance, relation to meals, or stage of pregnancy needs clarification. I certainly agree that serial studies of binding protein concentrations need to be measured in a carefully selected group of patients. I wonder, also, if the well documented increase during pregnancy in blood volume of approximately 30-50 percent and renal blood flow as well as other renal function measurements would affect significantly the clearance and elimination of a drug such as methadone. I would predict that methadone blood levels would be decreased during pregnancy on the basis of these normal physiologic changes and a decreased binding during pregnancy as shown by Dr. Szeto for the pregnant ewe. The larger volume of distribution of methadone in late pregnancy as reported from other studies seems generally consistent with increases in cardiac output, blood volume, and blood flow to various organs that occur normally during pregnancy and are most likely due to changes in progesterone and estrogen.

EFFECT OF PREGNANCY ON DISPOSITION OF OTHER NARCOTIC DRUGS

For other than meperidine, little information exists on the disposition of other narcotic drugs in pregnant humans. Hopefully, additional data will be presented for humans, but more importantly from basic animal experimentation using the chronic pregnant sheep preparation.

THE EXTENT OF FETAL DRUG EXPOSURE

I do not possess the expertise to comment adequately on the proposed two-compartment modeling, and will leave that for Dr. Perrier. The models for steady-state conditions for total (free and bound) drug indicate that fetal drug exposure would be determined by the clearance of drugs from mother to fetus and the clearance or elimination of the drug from the fetal compartment, either by placenta or nonplacental tissues. Obviously, the ideal drug is the one with the lowest placental clearance and the highest fetal clearance. It should be remembered that placental clearance relates only to that percent of the uterine or

umbilical flow that goes to area of maternal/fetal interface. From 5 to 15 percent of uterine and umbilical flow is distributed to the myometrium and membranes and does not participate to any extent in exchange from mother to fetus. Arterio-venous samples drawn upstream and downstream from this distribution of flows ignore these factors. It should also be recognized that the placenta itself contains many enzymes capable of metabolizing several substrates and therefore disposing or altering them. I wonder what percent of the maternal/fetal ratio can be accounted for by consideration of these factors.

METHADONE DISPOSITION IN THE MATERNAL-FETAL UNIT

Much of the presentation in this section has been discussed in the earlier section of this review. Further elucidation of the disposition of methadone in mother and fetus relates to the results of binding studies for maternal and cord plasma. The low ratios of fetal/maternal steady-state concentration of methadone of 0.15 and 0.18 for total drug concentrations and 0.40 to 0.42 for free drug have been explained by Dr. Szeto in her studies of fetal excretion of methadone by the fetal lamb. This is consistent with the observation of urinary excretion of methadone by the human newborn.

COMPARISON OF OTHER DRUGS IN THE MATERNAL-FETAL UNIT

The comparison of several narcotics in terms of maternal/fetal distribution by Dr. Szeto has indicated that morphine is better than meperidine and methadone in this regard but LAAM may result in the least fetal exposure, as reported by others (Man et al. 1980). While I agree with Dr. Szeto that it would be interesting to try to understand what contributes to morphine's low fetal exposure, it would hardly be the drug of choice in drug maintenance during pregnancy for many obvious reasons. The problem of distribution and disposition of metabolites of these various narcotics seems important to understand but difficult to design experimentally because of their lipid solubility and rapid bidirectional transfer across the placenta.

My comment regarding this section relates to the question of high organ exposure even though the general fetal exposure as measured by blood concentration is low. The best example of this is the distribution of LAAM, where extremely low fetal plasma concentrations with ratios of less than 0.11 in relation to maternal concentrations were associated with a much higher concentration in the brain than other organs (Man et al. 1980). As most of the clinically recognizable withdrawal symptoms in the human relate to central nervous system irritability, it seems important to determine not only maternal/fetal clearance and fetal clearance of any particular narcotic but to investigate specifically the blood/brain clearance, brain uptake, and effects on fetal brain function, metabolism, neuropathology, and long-term motor and mental development. I know that Dr. Szeto has looked at this question extensively and noted minimal, if any, changes in frequency and amplitude characteristics of the electroencephalogram following chronic drug administration. In an earlier study reported by us (Mann et al. 1976), in an acute preparation where drug blood levels were five to 10 times the steady-state concentration, the EEG became transiently isoelectric and was associated with a temporary but significant decrease in cerebral blood flow and a prolonged bradycardia. Those studies clearly represented an overdose situation, but nonetheless reflect significant brain uptake and effect on function at those drug concentrations. At drug concentration of .3 to .5 mcg/ml there seems to be no effect on fetal brain function as recorded from the continuous fetal EEG and only a minimal but not statistically significant elevation in heart rate. It would be interesting to know, however, what effect chronic dosing has on the ratio of high voltage slow activity/low voltage fast activity ratio. The development of deep sleep and REM sleep and associated physiologic variability during the last 2 to 3 weeks of gestation in the fetal sheep, where term is approximately 145 days, has been well described (Mann et al. 1974). I believe Dr. Szeto has preliminary information that indicates a loss of high voltage slow activity sleep during chronic steady-state administration of methadone and morphine. What effect this alteration in normal developmental ontogenesis of fetal cortical activity has on newborn and infant brain function represents an intriguing question most worthy of extensive investigation.

SPECULATION ABOUT THE DISPOSITION OF HEROIN IN THE MATERNAL-FETAL UNIT

The concept of the fetus acting as a sink for the metabolic products of heroin, 6-AM, and morphine is interesting and certainly needs further investigation. The pregnant sheep model is ideal for this type of study.

SUMMARY

A critical mass of information has now been accumulated that has provided us with a much better understanding of the disposition and metabolism of methadone and other drugs used for narcotic addiction maintenance during pregnancy. The justifiable and understandable barrier to further exploration of the question in the human maternal-fetal unit limits the potential for gathering significant additional information from this avenue of investigation. A well controlled clinical study that compares the outcome of a large number of addicted pregnant patients with a group maintained on methadone who have received good obstetrical care, diagnosis, and management needs to be conducted. Further exploration in the basic animal models should deal primarily with two critical areas of investigation: 1) the continued search for an appropriate drug that limits fetal exposure; and 2) the effect that all of these drugs have on fetal metabolism and function, particularly the fetal brain.

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DISCUSSION SUMMARY

Barbara Gastel, M.D., and Thomas E. Collins

The major topics of discussion in this session were the use of animal models such as sheep, topics of high priority for further research, and the complementary roles of animal research and clinical investigation.

Participants cautioned that the differences between sheep and humans must be considered in interpreting findings such as those reported by Dr. Szeto. It was mentioned, for example, that the placentas of sheep and of humans differ greatly and that methadone binds to the globulin fractions of plasma much more in humans than in animals.

The main suggestion for further research using the sheep model was to simulate the situation in humans more closely by continuously administering methadone and sometimes superimposing peak levels; Dr. Szeto noted that she is in fact now doing such work, by using an ambulatory pump. In addition, Dr. Kreek proposed performing cannulation for blood sampling across the liver, which appears to be important in the storage and release, as well as the biotransformation, of methadone.

Various members of the group emphasized the complementary roles of animal models and clinical research. Animal models, they stated, are useful for identifying possible effects of drugs such as methadone, exploring the mechanisms thereof, and sometimes in interpreting clinical observations. Furthermore, they noted, the findings obtained using such systems allow clinical studies, the scope of which ethical considerations limit, to be designed more wisely and efficiently. Thus, they concluded, this type of animal study is important even though the findings may not be directly applicable to patient care. At the end of the session, Dr. Blake observed that the approach being discussed had led to great advances in the chemotherapy of infectious diseases, and Dr. Finnegan called for mechanisms to bring together clinical and basic researchers to discuss opportunities for collaboration.

CHAPTER 2. METHADONE: TOXICITY, GENETIC AND PERINATAL EFFECTS

Monique C. Braude, Ph.D.

TOXICITY STUDIES WITH METHADONE

Methadone was developed in the 1940s as an analgesic. By the early 1970s, acute toxicology studies had been performed, but relatively little information was available on the drug's subacute or chronic toxicity in the tolerant animal. Because methadone was then being used or proposed for long-term, high-dose maintenance in man, NIDA commissioned chronic toxicity studies in animals.

Acute and chronic toxicity studies can demonstrate whether a drug's toxic effects are sufficient to preclude its administration to man. They can also alert clinicians to effects requiring special attention. Therefore, in toxicity studies, doses are chosen so as to produce some toxic effects at the highest dose level.

In evaluating the data from toxicity studies, it must be remembered that these findings are not directly translatable to human use. The doses used in animals are much higher than the expected clinical dose, and the life spans of man and the test animals differ, so that in an 18-month study in rats, the drug is administered for at least half the life span of the animals. Rodent mortality usually increases rapidly after 12 months, so that deaths in the second year may be due to aging, the drug, or both.

Acute toxicity studies of methadone show that the doses lethal in 50 percent of the animals (i.e., the LD_{50}s) vary with the species and route of administration. In the mouse, the LD_{50}s are 93.8 mg/kg orally and 9 to 17.3 mg/kg intravenously. In the rat, they are 90 to 95 mg/kg orally, 45 to 48 mg/kg subcutaneously, 23 mg/kg intraperitoneally, and 9.2 to 14.6 mg/kg intravenously. In the monkey, the LD_{50} is 10 to 20 mg/kg subcutaneously. Prior to the NIDA-supported studies, no data were available regarding the LD_{50} or chronic toxicity of methadone in animals dosed chronically (Wolven and Archer 1976).

Under contract to NIDA, two long-term chronic toxicity studies have been performed:

1) a chronic toxicity study consisting of an 80-week test period and an 8-week recovery period in rats; and

2) a 1-year chronic toxicity study in beagle dogs.

The designs of these studies followed the Food and Drug Administration (FDA) guidelines. Animals were divided into four groups: a control group, and low-, medium-, and high-dosage groups. In each group, hematological and clinical chemistry evaluations were done after 13, 26, and 52 weeks in the dog study and at the same intervals and after 79 weeks in the rat study. At the end of each period, some animals in each group were sacrificed for gross and microscopic pathologic examination to determine possible effects of the drug. Postmortem examinations were also performed on animals that died during the experiment.

The Rat Study

In the 80-week chronic study in rats, the doses of methadone were gradually increased to the final levels of 5, 10, and 20 mg/kg/day of methadone, given 7 days per week by gastric intubation.

The males receiving high doses gained significantly less weight than the control animals during the study but almost caught up during the recovery period. Food efficiency, calculated from mean body weight and mean food consumption data collected during the first 26 weeks of the study, did not differ between test and control animals. The mortality data show that many animals died, especially during the second year of the study, in both the control and treated groups. These deaths were attributed to naturally occurring respiratory infections and were not drug related. However, more males than females died in all groups except in the high dose female group.

Up to 10 mg/kg, no distinguishable pharmacologic or behavioral reactions were observed in test animals. However, increasing the dose to 15 or 20 mg/kg produced in some animals pharmacologic reactions such as "stupor-like" states, severe muscle rigidity, complete loss of the

righting reflex, and absence of both corneal and pain reflexes. Those reactions appeared within 15 minutes to 1 hour after dose administration and lasted up to 5 hours. All animals affected exhibited hypersensitivity to noise. Hyperactivity was noted at the lower dose levels, especially in the females.

In some treated males, mean serum glutamic pyruvic transaminase (SGPT) activities increased substantially starting between 26 and 52 weeks. Histopathological and pathological examinations did not reveal significant differences between treatment and control groups except for liver changes. These changes, present among several animals of both sexes in all test groups, consisted of hepatocellular hypertrophy and hyperplasia. The hepatic changes reverted to normal within 1 month after treatment was stopped. Separate experiments showed that these changes were probably related to an increase in N-demethylase activity produced by methadone and commonly encountered during chronic administration of drugs such as phenobarbital and diazepam, which are subject to hepatic metabolism.

The Dog Study

The 1-year chronic toxicity study in dogs was carried out with four groups of animals, as noted above, and included a 7-week recovery period during which animals not sacrificed were observed. Each group included eight males and eight females. All methadone groups were started at 2.5 mg/kg methadone given once daily in capsule form and increased by 5 mg/kg increments every 4 weeks to reach the final dose of 5, 10, or 20 mg/kg. No dogs died during the study.

Weight gain suppression was seen in all groups and was especially marked in the females. Sedation was noted at all dosages, was dose related, and lasted from 1 to 5 hours. Excessive salivation and emesis after dosing were seen in some animals at dose levels of 10 mg/kg and higher.

At these levels, some animals also showed hyperirritability, manifested in most cases by an abnormal aversion towards each other, which frequently resulted in fighting and in injuries requiring minor surgery. Hyperirritability became more common over time. Reduction of group size by the 6-month interim sacrifice did not appear to

relieve these symptoms. All abnormal behavioral reactions noted in the course of the study were seen in both males and females.

The two males and two females from each group maintained for the 7-week recovery period received empty gelatin capsules daily. None showed the emesis and salivation that had occurred immediately after dosing with methadone. Two animals that had received the highest dose level remained somewhat hyperirritable during the first week of recovery, but this behavior disappeared afterwards. In addition, on the first 2 days of recovery but not thereafter, these animals showed marked excitation when receiving the placebo.

Serum alkaline phosphatase levels increased in six of eight males dosed with 20 mg/kg/day but remained within normal values. Serum Ca^{++} was slightly elevated in females receiving 20 mg/kg/day. Urinalyses, respiratory rates, and the results of ophthalmologic examinations showed no abnormalities.

Electrocardiagram (EKG) tracings were taken after 4, 8, 13, 25, 39, and 52 weeks of testing and after 4 weeks of recovery. At the 5 mg/kg level, there were mild variations from the untreated control group. From 6 to 12 months, more significant changes such as increased heart rate (HR), increased ventricular complex, and S-T and T wave pathology were present; they disappeared after the 4-week recovery period.

At the 10 mg/kg level, four of eight dogs had heart rates above 180, one dog developed a heart block, and minimal S-T and T wave disturbances occurred for up to 6 months but were considered benign. EKG changes present in this group diminished with time; after the 4-week recovery, variations were within normal limits.

At the 20 mg/kg level, the changes were more consistent. The heart rate was elevated to 190 in five of eight dogs and to 210 in one. QRS changes in height and width occurred in three cases. Consistent T wave polarity changes were present after 3 months in the study and after the 6-week recovery period. These changes were not life threatening, and no pathology of the heart was noted after sacrifice.

All EKG tracings were reevaluated by an independent cardiologist, who reached the same conclusions: methadone

has some effect on the dog EKG at 10 mg/kg and above, but the significance of this effect and any hazard associated with it are uncertain.

After 6 or 12 months in the study, no treatment-related abnormalities in organ weights, gross pathology, or histopathology were seen at any of the doses tested.

GENETIC EFFECTS OF METHADONE

Because of the general acceptance and widespread use of methadone for treating heroin addicts, the question of whether this agent causes chromosome damage is of great importance. *In vivo* studies of the cytogenetic effect of methadone in humans have been confined to heroin or morphine addicts receiving methadone as a substitution therapy. In 1972, Falek et al. reported that at 72, but not 48 hours, cultures of leukocytes from multiple-drug users in a methadone maintenance program showed a significantly higher frequency of chromosome breaks than did those from a control population. In order to ascertain the drug responsible for this increase, *in vitro* studies were carried out with methadone, morphine, and quinine at various concentrations and durations of exposure; none of the agents induced any increase in chromosome breaks. In a second paper, Falek and McFadden (1973) reported that the increased level of chromosome damage persisted for up to 3 months after methadone maintenance was begun and then declined between 3 months and 1 year. In a follow-up study carried out after subjects had been receiving methadone for more than a year, the frequency of cells with chromosome damage had returned to a level comparable to that in controls. Former addicts in drug-free detoxification programs for over 2 years had similar decreases in chromosome damage.

In 1978, Matsuyama et al. reported the chromosome findings in 28 addicted veterans participating in a long-term double blind study designed to compare the effects of methadyl acetate (LAAM) and methadone. On admission to the study, subjects entered an 8-week stabilization period during which stable doses of the drugs were given. They then were assigned at random to one of three treatment modalities. Eleven subjects received 80 mg LAAM three times per week; eight received 50 mg methadone per day; and nine received 100 mg methadone per day. Although the investigators could not obtain age-matched, drug-free controls from the same setting, they included a

comparison group of younger male subjects who were neither chronic drug users nor taking any medication at the time of the study. Interestingly, although the other two groups included some polydrug users (checked by urinalyses), none of the subjects in the 100 mg/day methadone group reported the use of any other drug. After nearly 8 weeks, neither methadone nor LAAM produced any detectable increase in chromosome abnormalities. The percentage of cells with chromosome breaks was about 2 percent in each of the four groups; except for one translocation in one subject in the 50 mg/day group, all abnormalities were simple chromatoid or isochromatid breaks or fragments. Although the frequency of hypodiploid cells (cells with 45 or fewer chromosomes) was higher (15.3 percent) in the 100 mg methadone group than in the comparison group (9.8 percent), the difference was not statistically significant. As mentioned by the authors, it must be remembered that this study included only a small number of patients, and that no data are available for the drug groups prior to treatment. In addition, no longitudinal data are available, and the possibility of transient increases has not been ruled out.

In a letter to the editor of Archives of General Psychiatry, Falek and Hollingsworth (1980a) reviewed Falek's data and those of Matsuyama. They noted that the difference in reported results may be due to the greatest range of damaged cells in Matsuyama's comparison group, with zero to four breaks in 50 cells, i.e., 2.4 percent of breaks vs 0.4 percent in Falek's controls. Also, the finding of at least one person in a control population of 10 with four breaks in 50 cells may indicate a nonrandom distribution that could have produced the high number of total breaks in the cells of that comparison group. They also emphasized that (1) heroin use significantly increases the frequency of cells with chromosome damage over that observed in the general population, (2) chromosome damage is random among addicts and is not limited to a few persons, (3) the frequency of cells with chromosome damage remains increased for up to a year in persons in methadone maintenance programs, even though chromosome damage declines in rats after 3 months in treatment, and (4) after 1 year in methadone treatment or detoxification programs, the proportion of cells with chromosome damage declines to control levels. The chromosome breakage data are further supported by sister chromatic exchange (SCE) and DNA repair findings in opiate addicts, in patients receiving long-term methadone therapy, and in controls in Falek's laboratory. In the SCE studies, the SCE base

level in the 35 methadone maintained subjects did not differ significantly from that in the 39 controls.

In the DNA repair synthesis (DRS) study, blood samples from street heroin addicts and methadone maintenance patients were obtained from three programs: two in Georgia and one in Illinois. The influence of demographic factors, age, sex, coffee drinking, alcohol use, and tobacco smoking was also evaluated. DRS in leukocytes stressed by far-UV irradiation was studied in 90 normal individuals, 38 street heroin addicts, and 18 methadone maintenance patients. Age, sex, coffee drinking, and alcohol use did not significantly affect the maximal repair synthesis response of the control subjects, but smoking tobacco significantly decreased the mean response and variance. Heroin addicts showed an even more pronounced decrease, which may be related to the high rate of chromosome aberrations in this population. Half of the addicts tested could not repair UV damage in the 2-hour assay period. Long-term methadone treatment ameliorated the effects of the street heroin, just as it decreased the frequency of chromosome aberrations (Madden et al. 1979). Unfortunately, in none of these studies was the dose of methadone used in the patients reported.

Two papers on chromosome studies in infants born to mothers maintained on methadone during pregnancy have been published. As reported in 1975, Abrams studied peripheral blood chromosomes in 34 newborn infants who had been exposed to heroin and methadone *in utero*, and in 22 newborn controls. Compared with 14 controls, those 16 infants exposed predominantly to heroin showed a significantly increased frequency of chromosomal aberrations; however, those infants whose mothers had been taking more than 50 mg/day of methadone and their eight controls showed no significant difference in the incidence of chromosomal aberrations. Chromosomal rearrangements (dicentrics, rings, markers) were observed, however, in both drug-exposed groups, which led the author to suspect that heroin and methadone can induce chromosome damage *in vivo*. (Chromosome rearrangements rarely occur spontaneously in humans. Because they can be transmitted to future generations, they are considered more significant than breaks and fragments, which usually render cells nonviable.) The author points out that his results must be interpreted with caution, for the pregnant addict is exposed to various factors--including nutritional deficiencies, infections (to which the heroin addict is especially prone), chemical impurities in the

"bag" of heroin, and multiple drug use--that may damage chromosomes in the fetus. Any or all of these noxious influences may have contributed to the high incidence of chromosomal abnormalities in the heroin-exposed infants. By the same token, the low incidence of chromosomal abnormalities in the methadone-exposed group may reflect the improved lifestyle of the methadone-treated mother.

Another study on the cytogenetics of methadone-managed and heroin-addicted pregnant women and their newborn infants was published in 1976 by Amarose and Norusis and yielded different results. In this study in Chicago, chromosomal damage was assessed prenatally and at delivery. Cytogenetic samples were obtained from 99 addicted pregnant women (80 members of a methadone maintenance program and 19 heroin addicts) and from their 101 offspring. At delivery, samples of maternal and infant cord blood were obtained from all parents. The methadone dosage range was 0 to 8 mg daily with an average daily dose of 32.7 mg. Preparation of the 72-hour blood cultures was started immediately after the blood sample was taken. Nearly all cultures had 100 cells scored. In this study, about 10 percent of the cells scored showed chromosomal aberrations. Chromosome damage was random, affected all chromosomes, and was mainly of the acentric fragment type. The percent of hypodiploidy was significantly higher than that of hyperdiploidy. In the mothers, no significant differences were found with respect to dosage and duration of methadone treatment and years of heroin abuse. No significant association was found between maternal variables and infant chromosome damage, but infants with low Apgar scores (1 to 6) had cells with significantly higher levels of chromosome damage than did those with higher scores (7 to 10). Unfortunately, the results of this study are difficult to evaluate, as no control group was included.

Animal studies by Smith and Joffe (1975) have shown that acute subcutaneous administration of methadone to male rats prior to mating results in adverse effects on their progeny, particularly decreased birth weights, increased frequency of abnormally small litters, and increased neonatal mortality. A later study, where the animals were given methadone chronically (up to 20 mg/kg), indicates

that tolerance developed to the adverse effects observed acutely, as no adverse effects were found in offspring after 21 to 32 days of methadone administration (Soyka et al. 1978). Also, no evidence for a dominant lethal effect could be found after chronic administration by the same authors, in contrast to suggestive evidence for this effect found in previous experiments after acute methadone administration (Soyka et al. 1978; Badr et al. 1979). In addition, Badr et al. studied the spermatocytes of mice treated with 1 to 6 mg/kg of methadone intraperitoneally once daily for 3 consecutive days. Three distinct categories of chromosomal abnormalities were observed, which included chromosomal univalents, translocations, and poliploidy. When the total chromosomal aberrations per cell were calculated, a proportional increase in the total frequency of chromosomal aberrations was apparent at the doses of 1, 2, and 4 mg/kg, but there was a decrease at the higher dose of 6 mg/kg. No studies of the effect of chronic methadone administration on spermatocytes appear to have been reported.

A careful examination of methadone genetic activity was also performed under contract by the National Institute on Drug Abuse (1977) using a battery of *in vitro* and *in vivo* assays. A summary of the evaluation plan, consisting of a three-phase approach, is shown in table 1.

The interpretation and conclusions derived from the combined results were as follows.

Methadone produced weak activity in the E. coli DNA repair assay at the high end of the concentration range employed. Mutagenicity was also evident in assays with L5178Y mouse lymphoma cells and Neurospora crassa. The activity observed in the three assays was not strong, and only the Neurospora data could be considered conclusive, since the effect was clearly significantly different from expected spontaneous values. The E. coli and L5178Y mouse lymphoma cell results were both borderline for these assays. This spectrum of responses, however, must be considered as indicative of mutagenic potential for methadone since it was obtained in both prokaryotic and eukaryotic cell types. Absence of any *in vivo* responses reduces but does not eliminate the indication of human risk.

Table 1. Genetic effects of methadone

Phase	Test	Event detected	Results
I	S. typhimurium	Reverse gene mutation	Negative
	E. coli	Reverse gene mutation	Negative
	E. coli	DNA modifying effects	Positive (weak)
	S. Cerevisiae	Mitotic gene conversion	Negative
	N. crassa	Forward gene mutation	Positive
II	L5178Y mouse □ lymphoma cells	Forward gene mutation	Positive (weak)
	WI-38 human □ diploid cells	Unscheduled DNA Synthesis	
III	Rat bone marrow □ cytogenetics	Somatic cell chromosome □ aberrations	Negative
	Mouse heritable □ translocation	Germ cell chromosome □ aberrations	Negative

Another investigator (Legator 1982) also tested methadone in a variety of test systems, including the Ames test, for potential genetic effects. His results confirm those of the previous study. The Ames test was also negative for methadone. However, in vivo metaphase analysis of chromosomes from mice treated with 5 to 50 mg/kg of methadone produced a positive response. There was a dose related increase in chromatic breaks, centric fusions and gaps. There was also a statistically significant increase in the percentage of micronuclei in polychromatic erythrocytes in mice treated with 25 mg/kg of methadone orally at the 25 mg/kg but not at the 50 mg/kg level.

Conclusion and Future Research Needs

As in evaluating other effects of methadone, it is important to differentiate acute from long-term effects and to consider demographic and nutritional factors that could affect results. In most of the studies reviewed, long-term maintenance treatment seems to correct the genetic damage produced by heroin use.

As recommended by Falek and Hollingsworth (1980a), in genetic studies in which methods are still being developed, once initial results are presented, studies need to be established in other research centers using standardized protocols, similar supplies (including growth media, chemical, and drugs), and even aliquots of the same tissue for comparative investigations. The cooperating laboratories should receive funding to conduct a program of studies to determine the reliability of the initial finding. Furthermore, the experimental design, including sample size and statistical tests necessary to evaluate the data and to determine significance at desired levels of confidence, must be developed before the investigation. Too often, it seems, sample size is considered appropriate if the data produce significant results, but too small for proper evaluation if the statistical analyses do not demonstrate statistical significance.

These studies must be organized at both the preclinical and the human levels. Preclinical cytogenetic studies will enable more definitive findings about the *in vivo* effect of a specific drug in an animal (other than man) controlled at both the genetic and environmental levels. The difficulty, of course, is in extrapolating findings from other animals to humans. It is readily apparent that *in vivo* studies of drug abuse in humans are needed despite the many difficulties of establishing appropriate control samples. "Family medical and drug histories are never complete, and proof that an individual has not used the readily available social drugs of abuse is virtually impossible. Many of the above findings on the genetic aspects of drugs of abuse are, therefore, open to challenge. Standardized procedures and planned testing in cooperating laboratory programs are necessary to improve the reliability of, and enhance the confidence in, investigations of such drugs. Furthermore, equivocal findings may also be due to the relatively gross methods of analysis that have been used. To detect low levels of

genetic alteration, more definitive techniques are required; new procedures now are available to investigate such events at more basic levels.

Finally, methadone should not be considered "another opiate." It is structurally very different from morphine and probably binds to DNA in a very different manner.

REPRODUCTIVE STUDIES WITH METHADONE

Dr. Sparber's chapter (this volume, p. 318) reviews the perinatal biochemical, behavioral, and neuroendocrine effects of methadone on the development of the neonate, so I will limit this discussion to the morphological and reproductive aspects. I will cover in depth NIDA-supported studies and will highlight the most relevant findings from the literature.

Reproductive studies of methadone in rodents are numerous and have improved as new methodology, especially in the analytical and pharmacokinetic areas, became available in the 1970s. In addition to the NIDA-supported studies, most research in this area has emanated from a number of well established groups, such as those of Geber, Peters, Hutchings, Slotkin, and Zagon, who have published their data in referred journals such as the American Journal of Obstetrics and Gynecology, the Journal of Pharmacology and Experimental Therapeutics, Neuropharmacology, Pharmacology, Biochemistry and Behavior, and others.

The reproductive studies in animals that were initiated by NIDA and performed under contract in 1974-1975 will first be reviewed.

I. Reproduction-Teratogenic-Progeny Cross-Over Studies with Methadone in Albino Rats (NIDA 1975c).

This study was conducted to determine the effects of orally administered methadone on the fertility, the reproductive performance, and the survival of offspring in albino Charles-River rats. The teratogenic potential of the drug was also evaluated.

A. Methodology. A total of 460 rats (140 males and 320 females) 35 days old were used. The dose of methadone was 2.5 mg initially and gradually was increased to maximum daily levels of 5, 10, or 20 mg of methadone per kg

of body weight (table 2). Dosage solutions were prepared by adding distilled water to premeasured amounts of methadone. All doses were administered orally, via gavage. Control animals were given the distilled water.

All animals were treated at the designated escalating levels of methadone for 90 days prior to initiation of the mating period (table 2) and continued to receive their respective doses until completion of their portion of the investigation (sacrifice). All animals were allowed food and water ad libitum.

1. Reproduction and teratogenic studies. Individual body weights were determined daily for the purpose of dose administration. The body weight of each animal was recorded weekly throughout the premating period. Body weights of males continued to be recorded weekly through completion of the mating period, at which time the males were sacrificed and final body weights were recorded. Body weights of females were recorded at parturition; on days 1, 4, 12, and 21 of the lactation period; and 1 week postweaning (28 days postpartum). Daily observations for untoward behavioral reactions and mortality were conducted throughout the investigation.

After 90 days of exposure to methadone, each female was paired with a male from within the same group. Daily examinations were conducted to determine if copulation had occurred. Females used in the teratology portion of the experiment were removed from the breeding cages when vaginal smears confirmed the presence of sperm in the vagina. Males were rotated within their dietary groups at 10-day intervals until conception was confirmed or until each female had been paired with males for a maximum of 30 days. Records of fertility, mating ability, and reproductive performance were maintained.

Three parameters of fertility were calculated: 1) the fecundity index, 2) the male fertility index, and 3) the female fertility index. The fecundity index is the percentage of all copulations that result in pregnancy. Male and female fertility indices isolate potential impaired fertility to specific sexes. In calculating the male fertility index, only males having an opportunity to impregnate a fertile dam during the mating trial are included. The female fertility index is the percentage of pregnancies resulting from dams' having been paired with fertile males.

Table 2. Experimental design of the reproduction/teratogenic/progeny cross-over studies with methadone in albino rats

Group	Number of animals		Animals exposed to methadone*	Dosage escalation (mg/kg/day) Week:					
	Males	Females		1-2	3-4	5-6	7-8	9-10	11-Termination
Control	20	60	None	None	-	-	-	-	-
T-I M	20	40	Males	2.5	5.0	5.0	5.0	5.0	5.0
T-II F	20	40	Females	2.5	5.0	5.0	5.0	5.0	5.0
T-III M	20	40	Males	2.5	5.0	5.0	10.0	10.0	10.0
T-IV F	20	40	Females	2.5	5.0	5.0	10.0	10.0	10.0
T-V M	20	40	Males	2.5	5.0	10.0	15.0	20.0	20.0
T-VI F	20	60**	Females	2.5	5.0	10.0	15.0	20.0	20.0

*Animals not exposed to methadone were treated with distilled water.
**Twenty females utilized in the progeny cross-over study.

The indices employed were calculated as follows:

$$\text{Mating Index} = \frac{\text{Number of copulations*}}{\text{Number of estrus cycles required}} \times 100$$

$$\text{Fecundity index} = \frac{\text{Number of pregnancies}}{\text{Number of copulations}} \times 100$$

$$\text{Male fertility index} = \frac{\text{Number of sires}}{\text{No. of males mated with fertile females}} \times 100$$

$$\text{Female fertility index} = \frac{\text{Number of pregnancies}}{\text{No. of females mated with fertile males}} \times 100$$

$$\text{Incidence of parturition} = \frac{\text{Number of parturitions}}{\text{Number of pregnancies}} \times 100$$

*Only one copulation counted per estrus cycle. Five days equals one estrus cycle.

Twenty dams of each group were randomly selected to deliver and wean their litters. All pups were examined for physical abnormalities at birth, and the numbers of viable and stillborn members of each litter were recorded. Records of survival were maintained at various stages of the lactation period. Behavior and mortality were observed daily. At the weaning of each litter, each pup was again examined for physical abnormalities. Survival indices were calculated at birth; 1, 4, and 12 days postpartum; and at weaning (21 days postpartum). Litters of more than 10 pups were reduced to that number on the fourth day of the lactation period. Combined body weights of each litter were recorded at birth and at days 1, 4, and 12 of lactation; individual weights were recorded at weaning (lactation day 21).

For the teratology part of the study, 20 females of each group were randomly designated to have their pregnancies terminated on the twentieth day of gestation. They were sacrificed by carbon dioxide asphyxiation, an incision made in the abdominal wall, and the full extent of both uterine horns was exposed immediately. Fetal swelling and implantation sites were counted, special attention

being paid to resorption sites and uterine abnormalities. The number of corpora lutea was determined and recorded.

The number of fetuses in the uterus and their viability were determined. Each fetus was removed after cutting the umbilical cord, and the fetuses were weighed. After the sex of each fetus was determined, the total body weight for each sex was recorded by litter. The fetuses were examined externally, with special attention to detecting gross abnormalities. Each fetus was then examined either for skeletal development using alizarin staining or for internal development using the free-hand razor blade section technique of Wilson and Warkany. When possible, equal numbers of fetuses of each sex from each litter were examined by each method.

2. Progeny cross-over study (see table 3 for study design). Twenty control dams and 20 dams of the T-VI 20 mg/kg group were randomly selected for the progeny cross-over study. On the day of birth, entire litters of progeny exposed to methadone *in utero* were exchanged with entire litters of progeny obtained from control dams. The exchanged progeny (the groups designated by "B") remained with their foster mothers throughout lactation. Progeny born to the other groups stayed with their own mothers.

The above procedures pertaining to body weights, mating, mortality, reactions, and observations of progeny were again followed during this portion of the investigation.

At the end of the mating period in males and the lactation period in females, all parental animals were sacrificed and examined for gross pathologic anomalies. In addition, the gonads from apparently nonfertile animals, and any grossly abnormal tissues or organs noted at autopsy, were examined histologically.

Teratogenic evaluations were performed on the fetuses obtained from the sacrifices of females at day 20 of gestation. In addition, 10 male and 10 female weanlings of each test group were randomly selected for gross pathologic autopsies of 30 tissues.

From each test group, representative progeny that died during the lactation period were retained for possible pathologic examinations.

Table 3. Experimental design of the progeny cross-over study of methadone in albino rats

Group	Subgroup	Maximum number of dams	Maximum dose level* (mg/kg/day)	Neonatal exposure	
				gestation	lactation
Control	C-A	10	None	None	None
	C-B	10	None	+	None
T-VI	T-VI-A	10	20	+	+
	T-VI-B	10	20	None	+

*Maternal dose level escalation is shown in table 1 (group T-VI). The dose level of 20 mg/kg/day was administered from the ninth week of the investigation (5 weeks before mating) through completion of this portion of the investigation.

B. Results: 1. Reproduction and teratogenic studies. Throughout the study, males in the treated and nontreated groups showed similar body weights and body weight gains. Each group of dams given methadone displayed normal growth before mating, but females given 20 mg/kg exhibited slightly reduced body weights during the first 12 days of lactation.

None of the deaths appeared attributable to administration of methadone. However, pharmacologic reactions sometimes occurred among animals exposed to 15 mg/kg of the drug and became more frequent and more severe at 20 mg/kg. The affected animals exhibited a "stupor-like" state, were spasmodic at times, and displayed mild to severe muscular rigidity, convulsions, tremors, heavy salivation, loss of righting reflex, and absence of corneal and pain reflexes. After 4 months, the females treated with 10 mg/kg methadone displayed slight hypoactivity. No unusual behavior was observed among the control animals or those exposed to 5 mg/kg of methadone.

In each group of animals in which the males were given methadone, mating and fecundity indices were slightly lower than those of the control group; no relationship between the level of drug exposure and the extent of these reductions was apparent. The fertility indices of males given 5 or 10 mg/kg were also somewhat reduced, but those of the males exposed to 20 mg/kg methadone were essentially the same as in the controls. The group in which the females received 20 mg/kg methadone had slightly reduced mating indices, and those treated with 10 mg/kg had fecundity indices slightly less than those of the control group. All other parameters of reproductive performance were similar for test and control animals.

The effects of maternal drug exposure were as follows: The number of stillbirths was increased among each group of dams exposed to methadone, as was the percent of dams with one or more stillbirths. Likewise, the number of viable pups delivered by dams given 10 or 20 mg/kg of methadone was reduced. No reduction of progeny born viable was apparent among the dams given 5 mg/kg. During the lactation period, survival indices were similar for progeny of treated dams and those of controls. All pups delivered appeared outwardly normal and were free of untoward behavioral reactions. No intergroup differences in body weight were attributable to maternal exposure to methadone.

The effects of paternal drug exposure were as follows: Similar numbers of pups were delivered by dams sired by drug-treated males and the control dams. The number of stillbirths was not increased, but there was a slight increase in the percent of dams with one or more stillbirths among those sired by males given 20 mg/kg methadone. Survival indices of pups sired by males given methadone were similar to those of controls. One stillborn pup with micrognathia was delivered by a dam whose litter was sired by a male exposed to 20 mg/kg methadone. All other pups appeared outwardly normal and were free of untoward behavioral reactions. Each group of progeny sired by males given methadone exhibited increased body weight at weaning.

Numbers of corpora lutea, implantation sites, and viable fetuses were similar among test and control groups. However, the number of resorption sites was increased in each test group in which either the dams or the sires received 20 mg/kg methadone (T-V and T-VI). Parental drug treatment did not alter fetal body weights, nor were any

gross external abnormalities that could be correlated with the parental drug treatment noted. Development of fetal skeletal and internal structures was similar in the control and test groups.

2. Progeny cross-over study. After delivery, some of the litters delivered by drug-treated dams were exchanged with those from control dams, and the progeny remained with their foster mothers throughout the lactation period. Concurrent groups of progeny delivered by treated and control dams were retained by their natural mothers during lactation. Survival of the group of progeny delivered and retained by the drug-treated dams was reduced during the lactation period. This reduction of pup survival was not noted among the progeny of the similarly treated dams during the reproduction portion of the investigation. No intergroup differences of pup body weights were attributable to maternal exposure to methadone during gestation, lactation, or both.

II. Teratogenic Studies of Methadone in Albino Rabbits (NIDA 1974a, b).

Three perinatal studies were performed in New Zealand albino rabbits. The first two were designed to assess the teratologic potential of methadone in another species. In the first study, a low incidence (1.4 percent at 3 mg/kg and 2.8 percent at 10 mg/kg) of grossly abnormal fetuses was obtained from methadone-treated female rabbits. In view of the results, a second study was performed.

Groups of pregnant rabbits were treated with either 0, 3, or 10 mg/kg of methadone given orally in a gelatin capsule from day 6 through day 18 of gestation. Two positive control groups, receiving thalidomide at either 37.5 or 75.0 mg/kg, were included to demonstrate sensitivity to a known teratogen. All were sacrificed on gestation day 29. Each fetus was excised and given a complete gross examination; internal structure was studied, and skeletal development was evaluated.

Gross external abnormalities were seen in 5.7 percent (6 of 106) fetuses exposed to 37.5 mg/kg thalidomide and 24.2 percent (16 of 66) fetuses exposed to 75.0 mg/kg. The abnormalities included talipomanus, anurous condition, and other structural changes indicative of the teratogenic response to thalidomide.

Methadone-treated does lost weight during both the drug treatment period (days 6 to 18) and the gestation period (days 0 to 29); the response was most severe in the 3 mg/kg group. In this group, the number of resorption sites was increased, and the number of live young was decreased. However, animals in the group receiving 10 mg/kg showed neither a significant increase in resorption sites (embryotoxicity) nor a significant decrease in the numbers of live young, although both values were at the ends of the established normal response ranges based on historical controls. On gross external examination, no structural changes were apparent in the fetuses in the control group. Two of 59 (or 2.4 percent) of the fetuses from the 3 mg/kg treated does were malformed; one showed talipomanus and the other talipomanus with pes valgus. Two fetuses of 116 (or 1.7 percent) from those treated with 10 mg/kg displayed gross structural anomalies (acrania, and acrania with both talipomanus and umbilical hernia). Fetuses from the methadone-treated females showed no treatment-related alterations in internal organs examination or in the skeleton other than the skeletal abnormalities noted above.

The incidence of gross structural abnormalities in the fetuses following in utero exposure to methadone at doses of 3 or 10 mg/kg was low. However, changes have been observed in each of two separate, essentially duplicate, experiments. Thus, it is concluded that at doses approaching those causing early embryonic death, methadone can produce structural defects in the fetus. The response is not strong; quantitatively, it is difficult to distinguish from background levels and it is not correlated with dose; qualitatively, there is no single defect produced by the drug.

A third study was conducted to evaluate the effects on the offspring of administering methadone orally at levels of 5 (T-I), 10 (T-II), or 25 (T-III) mg/kg/day to tolerant albino rabbits during gestation. The animals received methadone for 12 weeks before breeding; dose levels were incrementally increased from 2.5 mg/kg/day during that period until the appropriate dose level was attained. For at least 3 weeks before breeding, the test animals were treated with the dose level used during gestation. Both a control group and a positive control group were included. The control animals received 20 mg/kg/day of lactose during the entire investigation. The positive control animals were treated with 50 mg/kg/ day of thalidomide on days 6 through 18 of gestation and with empty gelatin capsules on all other days.

The results in the positive control group demonstrated the susceptibility of this strain of rabbit to a teratogenic agent. The 24-hour viability index was reduced to 68.6. Seven positive-control fetuses (13.7 percent) exhibited some type of external abnormality (primarily talipomanus or craniofacial defects, and eight (15.7 percent) showed some type of skeletal abnormality.

The number of deaths was increased in the T-III group at 25 mg/kg/day; other dose levels did not affect mortality. The probable cause of death of most of the animals that died during the study appeared to be respiratory insufficiency or failure due to respiratory infection. Drug related reactions (lethargy and hypoactivity) were exhibited by one T-I doe during week 4 and two T-I does and one T-III doe during week 5; these reactions began 1 to 2 hours after dosing and lasted about 6 hours. The affected animals appeared normal on all other test days, and all other animals appeared normal throughout the investigation. No effects on body weights and weight gains that could be attributed to treatment with methadone were noted during either the prebreeding treatment period or gestation. The data related to reproduction (e.g., numbers of implantation sites, resorption sites, live young) collected at the time of sacrifice revealed no dose- or test material-related effects attributable to treatment with methadone.

The 24-hour survival of the T-III fetuses was reduced (the 24-hour viability index was 62.7). However, prenatal exposure to methadone did not affect the 24-hour survivals of the T-I and T-II fetuses. The mean body weights of the T-I, T-II, and T-III fetuses were considered normal for this strain of rabbit in this laboratory. One fetus obtained from a T-I doe had bilateral talipomanus, which has been seen in fetuses obtained from control New Zealand albino rabbits used in teratogenic studies in this laboratory. One fetus from a T-III doe had an umbilical hernia, a normal variant occurring spontaneously at a low frequency in this strain of rabbit. No external abnormalities were seen among the fetuses obtained from the control and T-III does. There were no dose or methadone related effects on the occurrence of fetal external abnormalities. Dissection of young obtained from does treated with methadone revealed no gross internal abnormalities. One T-I fetus (1.3 percent) exhibited a skeletal abnormality (bilateral misalignment of the carpals), as well as the gross external abnormality mentioned above. No skeletal abnormalities were detected in any of the T-II or

T-III fetuses. Observations of fetal skeletal development disclosed no effects attributable to prenatal exposure to methadone.

In summary, the NIDA studies show:

1. No teratogenicity in the tolerant rat when animals having prior long-term (90-day) exposure to methadone were given up to 20 mg/kg orally during gestation.

In the rabbit, however, structural abnormalities were produced in fetuses following in utero exposure to methadone at a dose as low as 3 mg/kg orally, but the effect was not dose related. When the rabbits were made tolerant to methadone, only one skeletal abnormality was detected at the low dose level and none in the 10 and 25 mg/kg groups, so that no teratogenic effect could be attributed to methadone.

A positive control (thalidomide), which showed teratogenic effects and against which results could be assessed, was introduced in the rabbit studies. From these data it can be concluded that, at doses approaching those causing early embryonic death, methadone is a weak teratogen in the rabbit.

The findings for the rat agree with those of Markham et al. (1971) and Hutchings et al. (1976; 1979), both of whom administered methadone in the same dose range and did not observe structural malformations. The only study that has reported congenital malformation in a different animal, the hamster, is that of Gerber and Schramm (1975). Giving a single subcutaneous injection of methadone on day 8, and using high doses of 31 to 185 mg/kg, they found dose related congenital malformations in many fetuses. The number of fetuses showing congenital malformations was higher than when the mother was treated with morphine or propoxiphene in the same dose range.

2. Increased incidence of stillbirths and resorptions. There seems to be general agreement that acute administration of methadone produces some embryotoxicity, i.e., increases in the number of stillbirths and resorptions, often leading to reduced litter size. These effects usually occur at the higher dosages, about 25 to 40 mg/kg orally and 5 to 7.5 mg/kg intraperitoneally (Buchenauer et al. 1974).

In the NIDA studies, the number of stillbirths and the percentage of dams with stillbirths were increased in the 10 and 20 mg/kg rat groups. Hutchings et al. (1976) and Chandler et al. (1975), who also gave methadone orally to rats, likewise reported this finding. Interestingly, the percentage of resorptions was even greater in a group of 15 rats that had received physical dependence-producing doses of methadone for 41 days (30 mg/kg/day, p.o.) and were then suddenly withdrawn from methadone. This finding shows that methadone can have long-term effects in pregnancy, even once it is no longer being administered. However, the number of animals included in this group was small, only one high dose was used, and the study was not repeated using a larger number of animals. Markham et al. (1971) also found some increases in the number of fetal resorptions.

In the rabbit, an increase in resorption sites was seen at 3 mg/kg in one study but not at 10 mg/kg in the same study, and 25 mg/kg in the other.

3. Parental effects. In the NIDA rat study, no dam died, even in the group receiving 20 mg/kg orally.

However, Chandler et al. (1975) reported 12.5 percent mortality at 30 mg/kg and 0 percent at 25 mg/kg. The LD_{50} was sex dependent: 86 mg/kg for mature female and 102 mg/kg for mature male rats. Chandler is also the only one reporting dose-response curves for lethal and analgesic effects; the AD_{50} was approximately 17 mg/kg.

Hutchings et al. (1976) who gave 5 mg/kg methadone starting on day 8 for 4 days and increased the dose to 10 mg/kg from days 5 to 22 of gestation, reported a maternal death rate of 45 percent.

Buchenauer et al. (1974) have shown that 5 mg/kg intraperitoneally can be nontoxic in nonpregnant females but can produce a death rate of 50 percent in pregnant does. Giving 20 mg/kg divided into two equal doses/day subcutaneously during gestation was associated with death in 6 of 12 females (McDonald et al. 1975). Even though the animals had been made methadone dependent, the dose was still toxic by this route.

Various authors have reported reduction in maternal body weight, and the effect of methadone on food and water consumption has been studied. White et al. (1978) gave 5 mg/kg methadone daily intraperitoneally before mating and

during gestation and lactation. Methadone treated females had lower body weights through gestation (especially during the first 2 weeks) and lactation, but the deficits were not caused by consuming insufficient food and water.

Interestingly, this laboratory reports that the effect of methadone on water consumption varied with the reproductive state of the animal. Water intake during the total lactation period was significantly greater in methadone treated females than in saline treated controls (Field et al. 1977). These changes in water intake during the perinatal period should be taken into account if one decides to administer methadone in drinking water.

4. Neonatal effects. Many investigators have reported growth retardation, reduced litters, and reduced number of neonates. Again, these effects are related to dose, state of the individual (tolerant or nontolerant), presence or absence of withdrawal, and nutritional status (Crofford and Smith 1973). Chronic methadone treatment before, during, and after gestation tends to cause a reduction in overall growth rate that can still be seen in 10- to 12-week-old animals. In chronically treated animals, overall brain growth and brain protein content show a similar reduction (Peters 1977). Zagon and McLaughlin (1977) report that rat pups subjected to methadone (5 mg/kg intraperitoneally) during gestation or lactation were the most severely affected, with reductions in brain (12 percent and 30 percent, respectively) and cerebellar (27 percent and 29 percent, respectively) weight recorded at weaning. These disturbances in brain growth may occur after methadone exposure ceases.

CONCLUSION AND FUTURE RESEARCH NEEDS

During the past 12 years, much valuable information has been gathered on the genetic and perinatal effects of methadone. Depending on the questions asked, the dose and type of treatment (acute or chronic) should be carefully chosen. For perinatal behavioral studies, for instance, doses that are not toxic to the mother or the neonate should be used. Factors such as stress produced by repeated injections, especially intraperitoneally in a pregnant dam, should be evaluated, as should the nutritional and environmental factors that may influence results. At least in the rat, we now seem to have sufficient information regarding methadone perinatal effects

on reproductive factors. Recent research is seeking the biochemical and neuroanatomical causes of these effects; in this difficult area, more basic information is definitely needed, especially on the long-term delayed effects of methadone.

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CRITIQUE

David Blake, M.D.

Dr. Braude has presented examples of studies of methadone's effects on genetic, embryonic, and reproductive processes. It should be noted that the examples selected are a fraction of the published papers on this subject, although I believe they are representative. Because of the selectivity of the review, I thought it best to restrict my remarks to difficulties in interpretation of these studies and the interrelationships between mutagenic, teratogenic, and reproductive toxic effects.

Figure 1 presents a schema illustrating how mutagenic events can result in sterility, abortion, embryopathy (teratogenesis), malignancy, and aging, depending on the type of cell affected. Thus, it is possible that the entire spectrum of reproductive abnormalities can result from mutagenic effects although epigenetic mechanisms are alternate explanations. It can be seen that only those mutations which do not result in death of the affected cell can cause such effects. Propagated mutations in gametes, ova, or spermatozoa are most likely to result in sterility or early spontaneous abortion. The "dominant lethal" effect of a mutagen when given to male animals is an example of this propensity; survival of resultant embryos is relatively unlikely. If survival occurs, malformed offspring or second generation effects are likely. In the studies cited by Dr. Braude (Abrams 1975; Amarose and Norusis 1976) on human offspring of the methadone treated mothers, chromosomal studies did not demonstrate unequivocal evidence of mutations. However, chromosomal analysis is a relatively insensitive means of detecting mutations, which can occur at single loci without altering the karyotype. The studies of methadone's effect on progeny of exposed male rats (Smith et al. 1975; 1976) showed primarily growth inhibition, although litter size was decreased. While reduced litter size is an expected effect of mutation, there are many other mechanisms--including reduced maternal food intake--and thus the effect can be nonspecific. From these cited studies, and others of which I am aware, the evidence of mutagenic activity of methadone is at best equivocal. If methadone is a mutagen, it has very weak efficacy for the effect.

The teratologic studies with methadone also have produced equivocal results. In the tolerant rat and rabbit, no teratogenic effect was observed. In nontolerant rabbits, a small but dose-unrelated increase in malformations was observed. There may be a loss in the power of detecting teratogenic effects of drugs when the traditional separate analysis is made of reduced litter size (aborted embryos), resorbed fetuses ("aborted" fetuses), and malformed fetuses (teratogenic effect). Because it is possible that the ultimate fate of an affected embryo might be early or late abortion, or malformation, these are not necessarily mutually exclusive events. The term embryopathy is more global and includes all of these adverse outcomes. The consequence of separate classification of components of the total embryopathic outcome is to produce false negative results or to preclude the establishment of dose related effects. For example, with many teratogens, as the dose is increased, malformed fetuses are less likely because of an increase in resorbed fetuses. Schumacher et al. (1968)* demonstrated log-linear dose related embryopathic effects of thalidomide when the data were analyzed as the total embryopathy. Debate abounds on the interpretation of teratologic results. The literal meaning of a teratogenic effect is a gross structural malformation, i.e., dysmorphic effect. The studies to date with methadone in laboratory animals suggest that the drug has little, if any, true teratogenic effect. Since these studies do, however, suggest that the drug induces resorptions, it would be of interest to reexamine the data utilizing the total embryopathy as the dependent variable.

Regardless of the outcome of the suggested reanalysis, it should be realized that embryopathy could be the result of maternal effects, rather than direct embryo toxicity. It is very difficult to differentiate direct from indirect embryopathic effects, although a clear separation between the toxic dose to the embryo from the toxic dose to the mother would suggest the former. In view of the fact that the dose levels utilized in the teratologic studies were close to the maximum tolerated maternal dose levels, any fetal effects could quite likely be of the indirect type.

* Schumacher, H.; Blake, D.A.; Gurian, J.M.; and Gillette, J.R. A comparison of the teratogenic activity of thalidomide in rabbits and rats. J Pharmacol Exp Ther 160:189, 1968

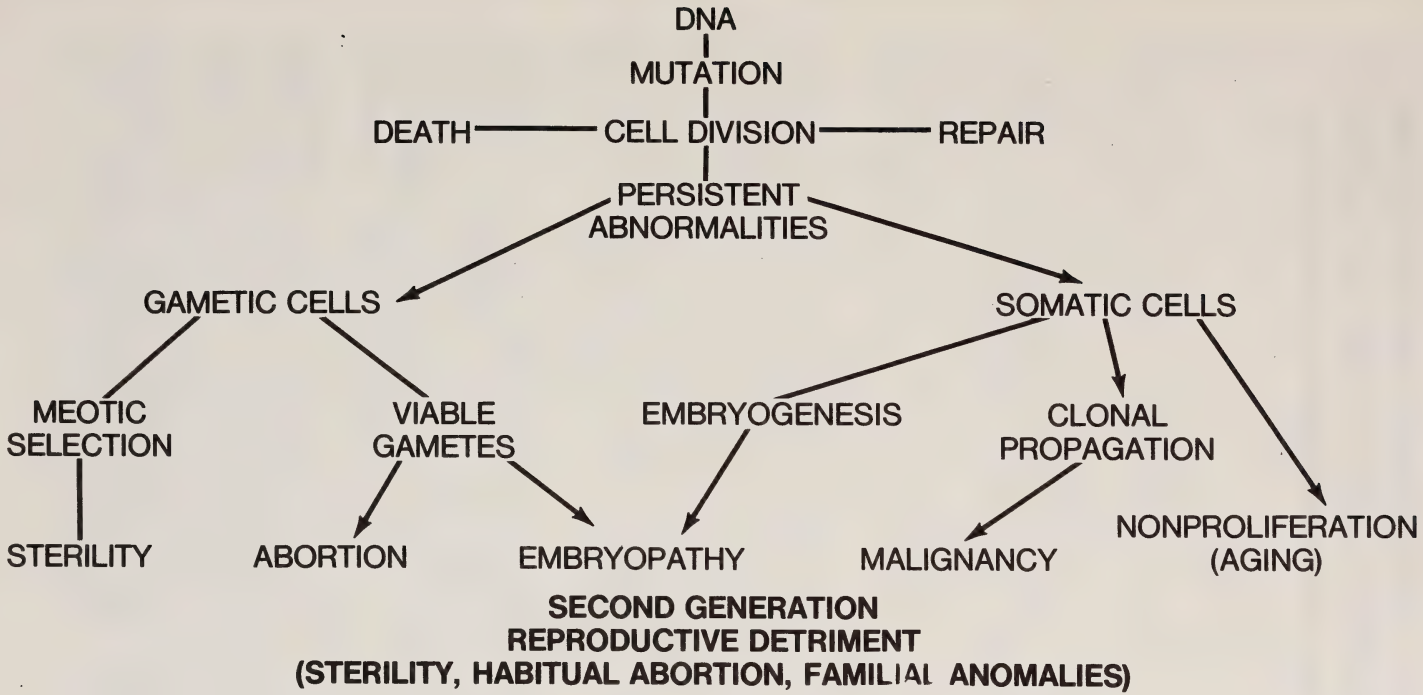

Figure 1. Clinical progression of mutagenesis

CHAPTER 3. PRECLINICAL PERINATAL AND DEVELOPMENTAL EFFECTS OF METHADONE: BEHAVIORAL AND BIOCHEMICAL ASPECTS

Sheldon B. Sparber, Ph.D.

Although perinatal and developmental effects of methadone in humans will be discussed later in this volume, infrahuman developmental studies actually followed, for the most part, clinical reports from the methadone maintenance experiences of the 1960s and early 1970s. Great "similarities" exist between the early reports on neonatal mortality and morbidity of addicted infants and the results of animal studies that followed (vide infra).

Generally, the most remarkable effect in the human neonate is the protracted and difficult-to-treat withdrawal syndrome (Reddy et al. 1971; Rajegawda et al. 1972; Finnegan 1976). However, few if any of the animal studies pay more than lip service to the possibility that perinatal abstinence may be an important determinant of the outcome of exposure to opiates during development. Only recently has this problem been addressed in the laboratory. One such study demonstrated that naloxone-induced withdrawal in both pregnant ewes and their fetuses altered sympathetic and parasympathetic function, leading to blood pressure, heart rate, arterial blood pH, and pO_2 changes, as well as meconium in amniotic fluid (Cohen et al. 1980). In other recent studies, withdrawal in opiate dependent chick fetuses, *in ova*, significantly decreased hatchability and survival in otherwise healthy but dependent subjects that would have hatched normally (Kuwahara and Sparber 1981); and morbidity and mortality increased in rat neonates born to mothers put through daily episodes of naloxone-induced withdrawal during the last trimester of pregnancy (Lichtblau and Sparber 1981a). Although continuous infusion of morphine (Cohen et al. 1980) or continuous exposure to l-α-acetylmethadol or its active metabolites (Kuwahara and Sparber 1981; Lichtblau and Sparber 1981a,b) was used in these experiments, no reason exists to believe that methadone dependence would have conveyed an altogether different outcome. Indeed, too rapidly reducing the dose of methadone given pregnant women can and does induce *in utero* abstinence (Stryker, personal communication).

Another problem associated with some of the behavioral, neurochemical, and endocrinological alterations being reported and reviewed here is that associated with the inappropriate doses and routes of methadone administered to animals during or shortly before pregnancy in studies purported to be models for the clinical situation. Consideration of these factors is extremely important, for they raise the possibility that many, if not most, of the congenital effects reported may be epiphenomena secondary to inappropriate experimental design or animal modeling, and therefore amenable to manipulation by altering treatment regimens, etc.

If many of the effects are indirect and controllable, it is important to demonstrate this. Otherwise methadone (or another clinically effective opiate) may erroneously be labeled a functional teratogen and its use inappropriately restricted, which could force the pregnant opiate addict back to the illicit heroin market, with all of its consequences.

EVIDENCE OF FUNCTIONAL TERATOGENESIS AND DIRECT POSTNATAL EFFECTS

Instead of reviewing each study in which the effects of pre- or perinatal exposure to methadone, on an unconditioned or conditioned behavior or biochemical variable, have been assessed, I will direct those interested in particulars to the appendix, which summarizes the relevant preclinical literature.

In general, the data seem real and believable. However, since the early reports of Buchenauer et al. (1974) and Chandler et al. (1975), which indicated that giving methadone to pregnant rats can retard fetal and postnatal growth and increase mortality of dams and offspring, no real new information has appeared.

It is both enlightening and disturbing that nobody has attempted to create in animals a model that closely parallels the clinical exposure of pregnant women and their fetuses, nor has anyone gone beyond the correlational analyses to design experiments that might help answer such questions as: Why are dams exposed to methadone and their neonates dying? Can pregnant animals be maintained on opiate dependence-inducing and blocking dosages without causing increased morbidity, mortality, or abnormal neurobehavioral development and function?

By far the most prolific laboratory reporting effects of methadone during development on neuroanatomical, neurochemical, neurobehavioral, and physiological variables is that of Zagon, whose most recent papers deal with thermoregulation and nociception in adult rats perinatally exposed to methadone (Zagon and McLaughlin 1980; Zagon and McLaughlin 1981). I have chosen to concentrate on this laboratory's reports because they are typical in most respects of the others listed in the appendix.

DOSE, ROUTE, AND FREQUENCY OF METHADONE ADMINISTRATION: ARE THEY APPROPRIATE?

Although I am certain that our clinical colleagues will say that it appears most prudent to reduce the dose of methadone in pregnant women to a level compatible with maintenance without subjectng the mother or fetus to withdrawal, the amounts of methadone used in all of the animal studies appear to be increased during pregnancy to keep the mg/kg dose constant (sometimes after one or two initial priming doses), even though the placental/fetal mass may cause a pregnant rat to attain 150 to 200 percent of her pregestational body weight. Although increasing absolute amounts or even raising the dose (mg/kg) may be rational if increased metabolism, placental/fetal sequestration, or other factors justify it, I am aware of no studies clearly showing such a need. We have successfully induced dependence on LAAM several weeks prior to mating rats and maintained them throughout pregnancy at the dose which is based on body weight at the time of conception. Although higher doses of LAAM (given orally) may retard body weight gain before and sometimes during pregnancy, such large doses are not needed to induce dependence of the opiate type in both mother and neonate. Lower maintenance doses are sufficient and do not induce morbidity and mortality in the dam and/or offspring (Lichtblau and Sparber 1981; Sparber and Lichtblau, in press). However, all studies reported by Zagon and coworkers have used a single daily dose (5 mg d,l-methadone/kg, intraperitoneally) that resulted in lower body weights throughout pregnancy. These authors claim that food consumption did not differ between treated and control dams, whereas water consumption was at times higher or lower for the treated females (White et al. 1978). Although these investigators must be credited with starting methadone treatment 5 days prior to mating the females, instead of sometime during gestation, as many others do (see appendix), they still have not

shown that their route and frequency of administration provide a reasonable model for the clinical experience.

The behavioral, analgesic, and plasma halflives of methadone administered to rats, even orally, are so short (about 1 to 5 hours) that injecting rats once per day with 5 mg/kg is probably producing acute toxicity, followed by episodic withdrawal sometime before the next dose. We have shown that this is so with morphine injected every 12 hours (Gellert and Sparber 1979), and no reason exists to believe the situation differs in rats dependent on and injected daily with methadone. Indeed, Dr. Kreek has recently reported that methadone maintained humans show endocrinological changes which may be interpreted as evidence of withdrawal before the next daily dose: 24 hours after the previous dose of methadone, plasma cortisol levels are elevated threefold (Kreek et al. 1981). Likewise, plasma corticosterone levels are elevated during precipitated withdrawal, as well as 12 hours after a dose of morphine in rats injected twice per day (Sparber et al. 1978).

In a study to test responsiveness to thermal and nociceptive stimuli in adulthood after being "perinatally exposed to methadone" (Zagon and McLaughlin 1980; Zagon and McLaughlin 1981), rats injected with 5 mg d, l-methadone/kg i.p. (the same dose and route used in the developmental studies) were described as "subdued having shallow ventilatory movements and often exhibiting plastic rigidity of posture." This supports my contention that an acutely toxic dose is being used by Zagon and other laboratories. Rats exposed to methadone and/or its direct and indirect effects upon respiration, nutrition, etc. were reported to have an altered basal temperature and show altered thermoregulatory responsiveness to the challenge (acutely toxic) dose of methadone at 120 days of age. Another striking feature of their results is that at 120 days of age both before and after acute methadone treatment, sensitivity to a hot plate (temperature not specified) is diminished to varying degrees, depending on sex and perinatal treatment. Imagine the possible tissue trauma of retesting rats after allowing them to remain on the hot plate for 30 seconds when control latencies are about 6 seconds. The confounding variable of a double retest under these conditions is not addressed. Furthermore, this laboratory has not reconciled their results showing what they call enhanced sensitivity to the antinociceptive effects of methadone with several other reports showing "tolerance" following prenatal or

early postnatal administration of morphine (Johannesson and Becker 1972; O'Callaghan and Holtzman 1976) or other opiates (O'Callaghan and Holtzman 1977). To add to the confusion, it has even been reported that administration of morphine to rats and mice only prior to conception will convey "tolerance" to morphine in offspring (Friedler and Cochin 1972; Friedler 1974). Because of the great differences in experimental design, agent, and time of treatment among the various laboratories, it is almost impossible to compare and contrast results in a meaningful manner.

I believe we all consider it imprudent to begin treating a pregnant woman with any drug after conception if other alternatives are available. It is also undesirable to expose a nonpregnant woman who may become pregnant within a few days to the pharmacological and toxicological consequences of a potent drug, if they may last long enough to threaten normal implantation, growth, and development. Since most of the animal studies use one or both of these procedures, it seems to me that most of the animal literature is irrelevant to the central question: Do methadone tolerant/dependent subjects' offspring, or animals used in model experiments of the above, show evidence of functional teratogenesis? The implication is that opiates directly affect growth and development, so that exposure to any treatment regimen could produce congenital effects. Conversely, if the clinical and experimental "deleterious" effects could be shown to be secondary to inappropriate treatment regimens or experimental design, adjusting dose or frequency may suffice to eliminate them.

DISREGARD OF IMPORTANT SUGGESTIONS

In 1975, Chandler and coworkers published an intriguing paper (Chandler et al. 1975) showing that a rather high dose of methadone (25 mg d,l-methadone/kg), administered orally by daily gavage for 10 days before mating and throughout gestation, significantly retarded fetal growth.

Interestingly, delayed parturition, with significantly increased birthweights, was also reported for females allowed to deliver instead of having their litters taken by cesarean section. Unfortunately, few if any investigators took the leads and suggestions in this paper and expanded and/or modified their procedures to study so-called behavioral teratogenic possibilities resulting

from methadone administration. The following points of the paper should have led to more appropriate research strategies.

1. Protracted withdrawal from chronic, daily high-dose methadone (30 mg/kg/day orally for 41 days followed by 40 days off drug) interferes with normal implantation and embryonic/fetal maintenance and development; it significantly reduces litter size (by increasing the number of resorptions) even when females are gavaged with water instead of methadone beginning 10 days before and throughout gestation. Perhaps withdrawal abstinence or the acute toxicity of the high dose resulted in fertilization of "abnormal" ova or an altered endocrinological or uterine milieu unable to maintain the normal complement of implanted embryos.

2. Treatment for 10 days prior to mating seemed to induce some tolerance to a pronounced developmental delay. The detrimental effect was greater when the females were started on 25 mg, d,l-methadone/kg/day immediately before mating than when they were treated with the same dose for 1-1/2 weeks before mating.

3. The authors speculated that the observed effects could be generalized to nonopiate drugs and even nondrug manipulations. Factors that might interfere with maternal-fetal interaction and thereby retard fetal growth include fetal undernutrition caused by "decreased uteroplacental blood flow, reduced maternal food intake or both." The authors even speculated that direct effects on the fetus may be amenable to reduction "by maternal tolerance to its (methadone's) analgesic effects."

4. They also speculated that methadone acted as a spasmolytic agent on uterine smooth muscle, either directly or by interfering with neurohumoral actions (e.g., those of 5-HT). Their mention that progesterone can also delay parturition and thus induce abnormally high intrauterine growth before delivery should have led to an assessment of endocrinological effects of opiates in pregnancy.

ENDOCRINOLOGICAL FACTORS

It has become obvious in recent years that many classes of psychoactive agents alter, either directly or indirectly, the release of hormones such as luteinizing hormone, testosterone, estrogens and progesterone, ACTH, MSH, and cortisol and corticosterone. In addition, opiates and other drugs may directly affect primary or secondary sex-gland function (Cicero et al. 1975), but the extent of these endocrinological effects most likely depends on the dose and frequency of opiate administration, with tolerance, readaptation between doses, or both playing an important role. For example, although Cicero et al. report no correlation between serum testosterone levels (or other effects) and the dose of methadone being taken by their human subjects, the reported range of methadone doses (30-115 mg daily) belies the fact that a very small spread in doses (66.9 $\pm$ 3.6, M $\pm$ SE) was available for finding a clear-cut correlation. The heroin users, who were most likely less physically dependent on opiates and experienced more periods without opiates, showed much less evidence of dysfunction than did the methadone users. It is probable that lower maintenance doses of methadone would convey fewer changes in physiological and behavioral indices of sexual function, and that well maintained methadone users, without evidence of other drug use, do not have great fluctuations of endocrinological variables (Everett and Radford 1971; Cushman 1972; Cushman and Kreek 1974).

Interestingly, although a recent study (Johnson and Rosecrans 1980) shows that methadone blocks ovulation in the rat by what appears to be a centrally mediated action, the authors conclude that their data support the use of methadone for heroin addiction. This conclusion is based on the fact that the dose of methadone necessary to block ovulation was excessive (toxic), leaving the rats "cataleptic for several hours." Because so many women in methadone maintenance programs have regular menstrual cycles, become pregnant, and maintain pregnancy to term, the demonstration that excessively high doses of methadone block ovulation in the rat is moot. However, I introduce this material to demonstrate the clinical inapplicability of studies in which a significant effect on function is obtained, with clinically irrelevant doses or procedures.

In one study in which excessively high doses of morphine were given at various times during gestation, fetal

wastage was great. Coadministration of progesterone significantly attenuated the severe consequences of the opiate treatment, demonstrating the potential importance of maintaining a stable endocrinological milieu during drug treatment (Temma et al. 1978). A series of studies in which male rats were treated with methadone before mating also speaks to the potentially important effects of drugs on endocrinological and target-organ function related to reproduction and development. Smith and Joffe (1975) have reported that treating males with methadone for about 2 weeks before mating them resulted in sundry effects on their progeny, including growth deficits and neonatal death. Treatment for longer periods prior to mating caused significant tolerance to the effects on the offspring (Soyka et al. 1978). Coadministration of testosterone with methadone likewise attenuated the effects (Soyka et al. 1980), demonstrating the importance of adequate modeling (i.e., chronic treatment before mating) if experimental questions related to the clinical methadone experience are being posed.

BIOCHEMICAL EFFECTS OF EXPOSURE DURING DEVELOPMENT

The relatively sparse literature on the biochemical effects of methadone exposure during development is equivocal and difficult to interpret. A few laboratories have essentially replicated and extended the original observations of Steele and Johannesson (1975), in which subcutaneous injection of 20 mg morphine/kg on days 17 through 20 or intravenous infusion of 20 mg morphine/kg over 4 hours on day 21 or 22 of gestation led to various changes both in DNA, RNA, and protein content of brain and in postnatal incorporation of radiolabeled thymidine, uridine, and amino acids into brain macromolecules. Whereas injection generally reduced macromolecular synthesis for several weeks after birth, infusion seemed to cause increased incorporation of radiolabeled precursors into brain macromolecules 2 weeks after birth. Interestingly, these authors report congenital tolerance in offspring of injected mothers and increased sensitivity to the analgesic effects of morphine in offspring of infused mothers. In similar studies, with immature and mature mice (Harris et al. 1975; Hui et al. 1978) to which excessively high doses of morphine or methadone were administered postnatally, similar alterations in macromolecular synthesis or content in brain and other tissue

(e.g., liver, skeletal muscle, heart) have been observed. It therefore appears that the immature subject, with rapidly differentiating and proliferating tissues, can have its macromolecular machinery altered by opiate exposure. However, this toxic effect is not restricted to immature subjects and may not even require potent analgesic (pharmacologic) activity, for the d-isomer of methadone (Jakubovic et al. 1978), as well as other agents (e.g., alcohol), is also capable of cellular toxicity of this type (Kuriyama et al. 1971; Tewari and Noble 1971; Noble and Tewari 1973).

NUTRITIONAL FACTORS

Although the concept of a nutritional deficiency need not be invoked to explain some of these effects (e.g., because high concentrations of these substances also alter biochemical parameters *in vitro*), the importance of nutritional status is raised by studies demonstrating a seeming lack of effect (e.g, of alcohol) on macromolecular machinery when nutritional factors are adequately controlled for (Jarlstedt 1977). Zagon's group has reported that in rats exposed to methadone either throughout prenatal development or during postnatal development until weaning at 21 days or both, there are highly significant reductions, at various ages, in brain weights and in protein, DNA, and RNA contents of brain. From a careful examination of this laboratory's data, some of which appears to have been published in four different reports (Zagon and McLaughlin 1977a, b; McLaughlin et al. 1978; Zagon and McLaughlin 1978b), it is obvious that the single daily dose of d,l-methadone (5 mg/kg, intraperitoneally) used in all of their studies (and/or whatever other factors come to bear on their results) is "toxic" enough to produce the following effects.

1. The weight gained by treated pregnant rats was significantly reduced, suggesting overt toxicity or malnutrition.

2. As shown by a more appropriate analysis, litter size was very significantly reduced, and its variability was significantly increased. Specifically, this group's data indicate that average litter size was reduced 25 percent and that many litters from treated dams contained relatively few pups. More than 60 percent of pups taken off drug at birth by being switched to nontreated foster mothers died, while

control pups placed on treatment via suckling from treated dams seemed to show the most growth retardation, whether measured grossly as body and/or brain weight or as protein, DNA, or RNA content of brain. In other words, what is obvious to this reviewer is that an inappropriate model was being used. On the one hand the survivor of severe postnatal withdrawal and on the other hand the survivor of neonatal opiate toxicity were being tested to determine if these procedures were potentially deleterious to offspring in ways other than reducing the survival rate to less than 40 percent.

Ford and Rhines (1979) treated pregnant rats with methadone during the last trimester of pregnancy and found the expected decrease in growth of the neonates for the entire 28-day observation period. In addition, cortical thickness and cell numbers of the neocortex were reduced during the first 2 weeks of life, with other measures of brain development showing effects for the entire observation period. Because treatment affected weight gain, a pair-fed control group was included. In neonates from this group, measurements of brain maturation were intermediate between those in the methadone treated animals and the ab lib-fed controls. Although the authors conclude that prenatal undernutrition may account for some of the growth reduction, they state that some is due to drug treatment. Possible indirect factors other than maternal undernutrition are not considered. However, placing a pregnant rat on a high dose of a potent drug that causes acute respiratory depression and endocrinological changes, and/or exposing her to the withdrawal associated with short-acting opiates, probably interact with any consequences of diminished food consumption. Also, because growth reduction probably is not the consequence of diminished food consumption per se, pair-feeding may not be the best control. A factor that has not been considered is neonatal, rather than prenatal, undernutrition. Many reports state that birth weight and size are unaltered in treated pups but that, during the first week or two, growth retardation becomes evident.

We have found that birth weight and size can be significantly reduced and neonatal survival decreased by subjecting pregnant opiate dependent dams to daily naloxone-precipitated withdrawal during their last trimester (Lichtblau and Sparber 1981a). Interestingly, although the pregnant rats lost a significant amount of

weight within hours after naloxone was injected, the syndrome abated enough before the next daily dose of naloxone so that, at term, weight gain by these dams did not differ from that gained by the controls. This observation implies that weight gain retardation in pregnant dams "maintained" on opiates probably reflects a more persistent alteration in the physiological or metabolic milieu than is induced by precipitated withdrawal.

DEVELOPMENTAL EXPOSURE AND BEHAVIORAL CONSEQUENCES

In the behavioral studies by Zagon's group, the effects of the exposure to the treatment and withdrawal regimens were confounded by the rats being picked up and dropped, exposed to strong auditory and olfactory cues, and so forth, daily during the first 19 days of life. The fact that a massive literature shows that stress and other aspects of early experience (e.g., handling) have pronounced behavioral effects in adulthood, as well as interacting with the appearance of development milestones, is neither considered in experimental design nor considered in interpreting the findings (Zagon and McLaughlin 1978a). It is quite amazing that the survivors of treatment (vide supra), with severe deficits in body and brain weight, as well as reductions of up to 50 percent brain DNA and up to 40 percent brain protein, could ultimately express all spontaneous behavioral and reflexive activities by 19 days of age. Not surprisingly, the authors state that "at this time, it is difficult to distinguish between a direct effect of methadone in regard to the alterations in preweaning behavioral maturation and a secondary effect related to other factors (e.g., undernutrition, stress, hormonal unbalance, abnormal palcentation, poor maternal care)." They explain away possible nutritional effects by stating that they did not find the significant reductions in litter size and birthweights often associated with placing pregnant rats on restricted diets. However, as stated above, my analysis of their data does show highly significant reductions in litter size. More importantly, their biochemical and behavioral reports indicate that perhaps the greatest effect on the pups may have resulted from postnatal factors. According to their own descriptions and interpretations of the neonates' behavior, the dose of methadone given the pregnant dams was "sufficiently high to precipitate the abstinence syndrome in neonates removed from drug exposure at

birth." Their reports also indicate that the pups exposed only via lactation may be affected at least as much as are the survivors of in utero exposure only, with those exposed continuously (in utero and during lactation) showing fewest effects. This further supports the importance of postnatal drug effects and other factors. For example, "offspring of the lactation group were observed to experience tremors from postnatal days 2 to 8" (Zagon and McLaughlin 1978a). Therefore, it should not be surprising that, in other studies, this group found many differences between controls and treated pups on unconditioned motor activities measured in the open field, photobeam activity cage, activity (running) wheel, and a step-down latency measure (Zagon et al. 1979a). Generally, biphasic results emerged, with exposed subjects showing first hypoactivity and then hyperactivity. Hardly surprisingly, differences also emerged (only female offspring were tested) on discrimination and active avoidance acquisition (Zagon et al. 1979b) starting at 120 days of age. However, in view of the severe perinatal experiences, the differences did not appear very great to this reviewer. When given adequate numbers of trials to reach a criterion, exposed offspring generally performed within limits of the control offspring. Therefore, although the authors claim that the results suggest that adult female rats perinatally exposed to methadone show deficiencies in acquiring, retaining, and/or performing learned responses, the deficiency seems mild when the biochemical and morbidity/mortality data are considered. Either the plasticity of the organism was sufficient to allow functional recovery or the task was not adequately chosen and/or utilized. This reviewer guesses that both were the case. Additionally, poor survival in one or more groups could have screened the samples, the most affected not surviving to be tested.

OTHER BIOCHEMICAL EFFECTS OF METHADONE EXPOSURE

In a series of experiments in which 5 mg methadone/kg was injected subcutaneously in rats, starting on day 10 of gestation, Slotkin's group has reported evidence of delayed maturation of heart and brain ornithine decarboxylase activity postnatally and precocious development of sympatho-adrenal function, measured as the ability of insulin hypoglycemic shock to induce neurally mediated cathecholamine release from the adrenal medulla (Slotkin et al. 1976; Slotkin et al. 1980b). Because postnatal

injection of methadone likewise enhanced the maturational process of adrenal release, the authors conclude that a prenatal critical period does not exist. Nor do they think that nutritional or behavioral effects of methadone on mothers is reponsible, for fostered pups also showed the effect. However, they fail to consider that non-treated foster mothers will behave abnormally toward abnormally behaving (opiate-intoxicated and/or withdrawn) neonates. Also, drug intoxication may lead the dams to neglect or even destroy offspring. A recent report suggests that this abnormal maternal behavior is the most prominent result of administering methadone to rats via drinking water (Grove et al. 1979). In the ODC studies (as in the release studies) and studies from other laboratories, significant maternal death, and weight gain retardation of dams and pups (neonates) are often secondary to methadone treatment. When Slotkin's group lowered the dose of methadone to 2.5 mg/kg, the maturational decline in brain ODC in rat neonates was not delayed, nor was brain growth significantly retarded. The median dose (2.5 mg/kg) did significantly reduce body and heart weight during the preweaning stage of growth. Therefore, it is not surprising that heart ODC showed the maturational delay after the 2.5 mg/kg dose. Because 1 mg/kg did not significantly alter body weight or organ weight, it may be that obvious growth retardation is not sufficient to alter ODC activity (Slotkin et al. 1980a), since 1 mg/kg did alter heart ODC in neonates. My objections to these studies again relate to the validity of the model and are identical to those stated above. Slotkin's group has shown only that treating nontolerant pregnant rats or neonates with a potent opiate can alter another biochemical variable. However, they have not demonstrated the maintenance (without withdrawal) capabilities of a single subcutaneous dose of methadone, nor have they determined if indirect effects (e.g., stress or corticosterone, due to acute opiate and/or withdrawal) can produce similar effects; heart ODC activity can be influenced by various stressors such as hypoxia, and brain ODC activity is influenced by steroids in neonates. An additional criticism relates to the fact that pregnant subjects were shipped to Slotkin's laboratory (and thus stressed), and that noninjected and/or pair-fed controls (hardly ever included by any laboratory) were not used. Starting treatment after conception or after birth may be valid only if a maintenance model is not being sought. There are so many confounding factors relating to adaptive processes (e.g., tolerance/dependence, withdrawal), endocrinological and nutritional status of

mother and offspring, and sundry other variables as to preclude using opiates as a tool to perturb developmental processes. Therefore, unless some unique characteristic of the opiate (e.g., methadone maintenance exposure) is a prime consideration, opiates probably should not be used for such experiments.

FUTURE RESEARCH NEEDS

By and large, what has been missing are studies designed to help answer specific questions relating to the many effects claimed to be direct consequences of opiate (methadone) exposure rather than to explore potential epiphenomena secondary to nutritional factors, acute overdose toxicity, and/or withdrawal. As previously mentioned, we have begun to explore some of these possibilities (Kuwahara and Sparber 1981; Lichtblau and Sparber 1981a). Behaviorally nontoxic but dependence inducing and -maintaining doses of an opiate can be shown to allow apparently normal growth and development, whereas higher doses given to pregnant rats will compromise the survival of the offspring (Lichtblau et al. 1980; Lichtblau and Sparber 1981b). Also, perinatal withdrawal will compromise survival and retard growth of fetuses addicted to opiates (Kuwahara and Sparber 1981; Lichtblau and Sparber 1981a). Most recently, we have found that removing normal, healthy rat pups from lactating mothers and giving them to nonlactating foster mothers for 3 of their first 6 days of life resulted in retarded body weight gain comparable in many respects to that reported again and again in the developmental methadone (and alcohol) literature. When these rats were mature, their basal rectal temperatures differed from those of littermates fostered to lactating rats, and their thermoregulatory responses to morphine differed from those of their normal-weight littermates. In addition, the dose-response curve describing the behavioral effects of morphine in the undernourished rats is biphasic: the rats seem "tolerant" to low doses and abnormally "sensitive" to a higher dose of morphine (Sparber and Lichtblau, 1983). These results are reminiscent of some of the previous data on thermoregulation discussed above and may explain the apparent discrepancy between Zagon's group, which found increased sensitivity to methadone's analgesic action, and other laboratories, which have reported congenital tolerance. Most importantly, our data demonstrate that one need not expose rats perinatally to opiates to alter their responsiveness to opiates in adulthood; it is sufficient to

modify their growth pattern in a manner similar to that afforded by opiate exposure or withdrawal.

We have also found that neonatal mortality resulting from congenital exposure to the longer-acting opiate -acetylmethadol (LAAM) can be increased from 52 percent to 88 percent by a single low dose of the antagonist naloxone on the first day of life, whereas a supplemental dose of LAAM and its active metabolites on the first day of life reduces neonatal mortality to 29 percent. The dose of naloxone did not affect 24-hour survival of control pups, but the dose of opiates increased mortality of controls from nil to 28 percent. Thus, the congenitally exposed pups were tolerant and in withdrawal within hours of birth (Sparber and Lichtblau, in press). This reviewer is convinced that such is also the case with methadone exposure--and more acutely so, because of the drug's shorter duration of action.

Lastly, we have recently found that injecting the potent opiate l-α-noracetylmethadol induced dependence without altering ODC activity in chick fetal brain. However, precipitating withdrawal with naloxone significantly increased fetal brain ODC activity (Kuwahara and Sparber 1983). Furthermore, dependent chicks hatching from eggs injected with the opiate have normal body weights but start to show growth retardation within a few days. Injection with naloxone on the third day of life significantly decreased heart ODC activity, whereas ODC activities in dependent chick fetuses and chicks injected with saline did not differ from those of controls (Kuwahara and Sparber, in preparation). Therefore, it now appears that exposure to dependence-inducing but otherwise nontoxic doses of opiates is not sufficient to alter brain and heart ODC activities, but that withdrawal induced by injecting naloxone can significantly change them.

From studies of the type just described, it is apparent that the wrong questions have continued to be asked concerning methadone (or any opiate) exposure during development. As stated in the introduction, if it can be demonstrated that tolerance develops to endocrinological and respiratory depressant effects of opiates, exposing experimental subjects for the first time near or during pregnancy is not a valid model for the clinical situation. If excessive doses and/or withdrawal are compromising the growth and maturation of developing subjects, adjustment of treatment regimens may reverse the effects. If more prudent and clinically relevant use of

experimental agents by basic biological scientists is forthcoming, it may be that advancement of our knowledge regarding the advantages and limitations of congenital drug exposure will move forward.

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Drug	Species	Dose (mg/kg)	Route	Duration	Maternal effects	Perinatal effects	Author
Methadone	rat	10	ip	days 19-21 gestation	distribution in pregnant different from non-pregnant	fetal brain concentration higher maternal	Peters et al., J.P.E.T. 181: 273-278, 1983
Methadone	mouse chick embryo	22-35 mg/kg mouse 0.75-5 mg chick	sc --	day 9 gestation inj at 28 hrs	not discussed	day 13 exencephaly (11.6%) spinal cord kinkage (34%)	Jurand, J. Embryol. Exp. Morph. 30: 449-458, 1973
Methadone	rat	2-7.5	ip	day 5 gestation until weaning	15-57% mortality	increased stillbirth and postnatal mortality; low birth, 7, and 14 day weights; normal at 21 days	Buchenauer et al., J.P.E.T. 189:66-71 189:66-71, 1974
Methadone	rat	25	po	throughout gestation 1 group 10 days prior to conception	not discussed	fetal growth retarded; excessive fetal size due to interference of parturition	Chandler et al., J.P.E.T. 192: 549-554, 1975
Methadone	hamster	31-185	sc	day 8 gestation or days 8-10	0-90% mortality	3-100% congenital malform; decrease number fetuses (86-185 mg/kg single inj)	Geber and Schrauma, Am. J. Obstet. Gynecol. 123:705-713, 1975
Methadone	rat	5	ip	1 wk before and throughout gestation	no effect on maternal wt gain	decrease no. live pups born/litter; increase postnatal mortality; higher drug concentration in fetal brain than maternal	Peters, J.P.E.T. 192: 513-520, 1975
Morphine Johannesson, Tox.	rat	20	sc	days 17-20 gestation; infusion day 21	not discussed	congenital morphine tolerance; altered brain DNA, RNA and protein; low body and brain wts.	Steele and Acta Pharmacol. et 36:243-256, 1975

Drug	Species	Dose (mg/kg)	Route	Duration	Maternal effects	Perinatal effects	Author
Methadone	rat	5-20 (in two equal doses a day)	sc	30 days before and throughout gestation	50% mortality	increased mortality no difference in growth rate of survivors	McDonald et al., Curr. Ther. Res. 17:308-317, 1975
Methadone	rat	5-20	po	day 8 gestation until birth	23% mortality at 10 mg/kg 56% mortality at 20 mg/kg decrease wt during gestation	decreased implant sites; increased prenatal mortality; low birth wts, no different at weaning	Hutchings et al., J.P.E.T. 197:171-199,
Morphine	rat	5 → 10 2x/day	sc	days 5-12 gestation	not discussed	low weaning wt in 1 of 3 experiments; congenital tolerance to morphine and levorphanol at 3, 5 and 11 wks	O'Callaghan and Holtzman, J.P.E.T. 197:533-544, 1976
Methadone	rat	2.5-5	sc	from day 10 gestation	not discussed	decreased body, brain and heart wt; delayed maturational decrease in brain and heart ODC	Stotkin, J.P.E.T. 199:141-148, 1976
Methadone	rat	2.3	po	10 wks before mating	not discussed	low birth wt, brain wt, brain protein; low protein and AChase at 21 days of age	Field et al., Arch. Int'l. P'codyn. Ther. 228:300-303, 1977
Heroin	rat	2.5-5	ip	5 days before mating and throughout gestation	not discussed	low birth wts and weaning wts; increased activity at 21 days of age	Lasky et al., Pharmacol, Biochem. Behav. 7:281-284 1977
Methadone	rat	5	ip	1 wk before and throughout gestation	not discussed, no fostering	decreased brain protein and RNA content; retarded acquisition of conditioned avoidance response	Peters, J.P.E.T. 203:340-346, 1977

Drug	Species	Dose (mg/kg)	Route	Duration	Maternal effects	Perinatal effects	Author
Levorphanol	rat	1 →1.75 2x/day	sc	days 5-12 gestation	not discussed	tolerance to morphine in 5-wk-old pups	O'Callaghan and Holtzman, J.P.E.T. 200:255-262, 1977
Morphine	rat	10 →40 5 days abstinent at mating	sc	last 14 days gestation	not discussed	94% postnatal mortality; low birth wt; increased motor activity in 15-30-day-old pups	Sobrian, Pharmacol. Biochem. Behav. 7:285-288, 1977
Methadone	rat	5	ip	5 days before and throughout gestation	not discussed	decreased body wt; significant mortality in pups removed from drug exposure at birth; retarded postnatal brain growth, no different at birth	Zagon and McLaughlin, Exp. Neurol. 56: 538-552, 1977
Methadone	rat	5	ip	5 days before mating and throughout mating	not discussed	decreased body and brain wts; decreased DNA at 21 days of age	Zagon et al., Experientia 33:1486, 1977
Methadone	monkey	0.24 l 0.24 d	im	early or late gestation	little placental transfer early much transfer late gestation, unchanged methadone		Davis and Fenimore, J.P.E.T. 205:577-586, 1978
Methadone	mouse	2	sc	to neonates	--------	Naloxone reversible inhibition of RNA and protein synthesis	Hui et al., Europ. J. Pharmacol. 49:87-93, 1978
Morphine	chicken embryo	0.4-8	-- air sac	days 3, 5, 7 embryogenesis	--------	log dose decreased survivability on day 15;	Jakubovic et al., Experientia 34: 1617-1618, 1978
Methadone		0.081 or 0.405	--	days 2-12 embryogenesis	--------	decreased brain protein concentration; decreased liver size	

Drug	Species	Dose (mg/kg)	Route	Duration	Maternal effects	Perinatal effects	Author
Methadone	rat	5	sc	5 days before and throughout gestation and/or lactation	not discussed	various organ and body wt differences postnatally due to all treatments (gestation, gestation-lactation, lactation)	McLaughlin et al., Biol. Neonate 34:48-54, 1978
Methadone Morphine	rat	5, 7.5	ip	1 wk before mating and throughout gestation lactation	not discussed	altered treadmill and shock avoidance with both drugs	Peters, Proc. West. Pharmacol. Soc. 24:411-418, 1978
Methadone	rat	10	sc	males treated 12 days prior to mating	--------	low birth wt and death	Soyka et al., Tox. App. Pharmacol. 45:797-807, 1978
Methadone	rat	2.5-20	sc	males treated for 21-32 days prior to mating	--------	tolerance to adverse effects on progeny (birth wt and neonatal mortality)	Soyka et al., Pharmacol. Biochem. Behav. 9:405-409, 1978
Morphine	rat	60-80 2x/day	sc	different days during gestation	prolonged pregnancy	fetal death, delayed development (reduced by progesterone)	Temma, Kitasato Arch Exp. Med. 51:41-46, 1978
Methadone	rat	5	ip	5 days before and throughout gestation and/or lactation	not discussed	altered brain chemistry at 10, 21 and 60 days of age	Zagon and McLaughlin, J. Neurochem. 31:49-54, 1978
Methadone	rat	5	ip	5 days before and throughout gestation and/or lactation	not discussed	altered behavioral maturation	Zagon and McLaughlin, Pharmacol. Biochem. Behav. 9:665-672, 1978
Methadone	rat	5	ip	5 days before and throughout gestation and lactation	decreased wt throughout gestation-lactation	decreased wt at weaning	White et al., Pharmacology 17:227-232, 1978

Drug	Species	Dose (mg/kg)	Route	Duration	Maternal effects	Perinatal effects	Author
Methadone	rat	1→5→1 2x/day	sc	from day 14 gestation until birth	decreased food consumption	reduced body, brain growth, cortical thickness and cell number reduced in brain; pair-fed group showed similar but less dramatic effects upon offspring	Ford and Rhines, Acta Neurol. Scand. 59:248-262, 1979
Methadone	rat	8-15	po (in drinking water)	from day 1 gestation	approx. 20% mortality	increased still-births, behavioral effects due to altered maternal rearing behavior; decreased open field behavior	Growth et al., Neurobehav. Toxicol. 1:87-95, 1979
Methadone	rat	5→10	po	from day 8 gestation until birth	45% maternal mortality; decreased wt gain during gestation	low birth wts; no different at weaning; high response output in various operant tasks	Hutchings et al., J.P.E.T. 208: 106-112, 1979
Morphine	rat	pellet	sc	neonate 5 or 11 days	--------	decreased adrenal response to morphine; low body wts; impaired maze learning	Sonderegger et al., Pharmacol. Biochem. Behav. 11 Suppl.:29-33, 1979
Methadone	rat	5	ip	5 days before and throughout gestation and/or lactation	not discussed	hypothermia decreased wt gain (gestation lactation)	Thompson et al., Pharmacol. Biochem. Behav. 10:551-556, 1979
Methadone	rat	5	ip	5 days before and throughout gestation and/or lactation	not discussed	less active at 21 and more active at 45 days of age	Zagon et al., Pharmacol. Biochem. Behav. 10:743-749, 1979
Methadone	rat	5	ip	5 days before and throughout gestation and/or lactation	not discussed	altered avoidance and discrimination	Zagon et al., Pharmacol. Biochem. Behav. 10:889-894, 1979

Drug	Species	Dose (mg/kg)	Route	Duration	Maternal effects	Perinatal effects	Author
Methadone Morphine	rat	4, 16	sc	day 8-22 gestation	2/5 mortality at 16 mg/kg	all offspring fostered to untreated dams; high mortality at 16 mg/kg; depressed open field activity (days 28-30)	Freeman, Intern. J. Neurosci. 11:295-300, 1980
Methadone	rat	5-10	po	day 8-22 gestation	decrease maternal wt with increased doses	prenatal mortality (10-17%); transitory sedation and hyperactivity days 2-5, offspring fostered to untreated dams	Hutchings et al., Neurobeh. Tox. 2:331-335, 1980
Methadone	rat	6-15	sc	proestrus	toxic dose prevented ovulation	--------	Johnson and Rosecrans, J.P.E.T. 213:110-113, 1980
Methadone	mouse	2.5-10	sc	last 6 days of gestation	reduced wt gain (10 mg/kg)	delayed delivery and smaller litters (10 mg/kg); more responses at higher fixed ratios (progressive fixed ratio); no congenital tolerance to methadone	Middaugh and Simpson, Neurobehav. Tox. 2:307-313, 1980
Methadone	rat	5 2x/day	sc	from day 5 gestation and/or lactation	not discussed	increased postnatal mortality; altered CA's in limbic and striatal regions in 21- and 90-day-old pups; altered avoidance behavior	Rech et al., Neurobehav. Tox. 2:75-78, 1980
Methadone	rat	1-5	sc	from day 10 gestation and/or lactation	not discussed	5 mg/kg - low body brain and heart wts; altered brain and heart ODC; heart ODC remained altered at lower doses	Slotkin et al., Life Sci. 26:861-867, 1980

Drug	Species	Dose (mg/kg)	Route	Duration	Maternal effects	Perinatal effects	Author
Methadone	rat	2.5 →5	sc	from day 10 gestation and/or lactation	not discussed	precocious sympatho-adrenal responsiveness	Slotkin et al., Life Sci. 26:1657-1663, 1980
Methadone	rat	5	ip	5 days before and throughout gestation and/or lactation	not discussed	elevated nociceptive threshold	Zagon and McLaughlin, Experientia 36:329-330, 1980
Morphine	rat	1	sc	single inj days 2, 5, 9 or 13	--------	delayed tolerance (paw lick latency on hotplate and open field activity after 5 mg/kg)	Bardo and Hughes, Develop. Psychobiol. 14:415-423, 1981
Methadone	rat	5	ip	5 days before and throughout gestation and/or lactation	not discussed	altered temp and nociception (sensitization) to analgesic effect of methadone 120 days of age	Zagon and McLaughlin, Life Sci. 29:1137-1142, 1981

CRITIQUE

Theodore A. Slotkin, Ph.D.

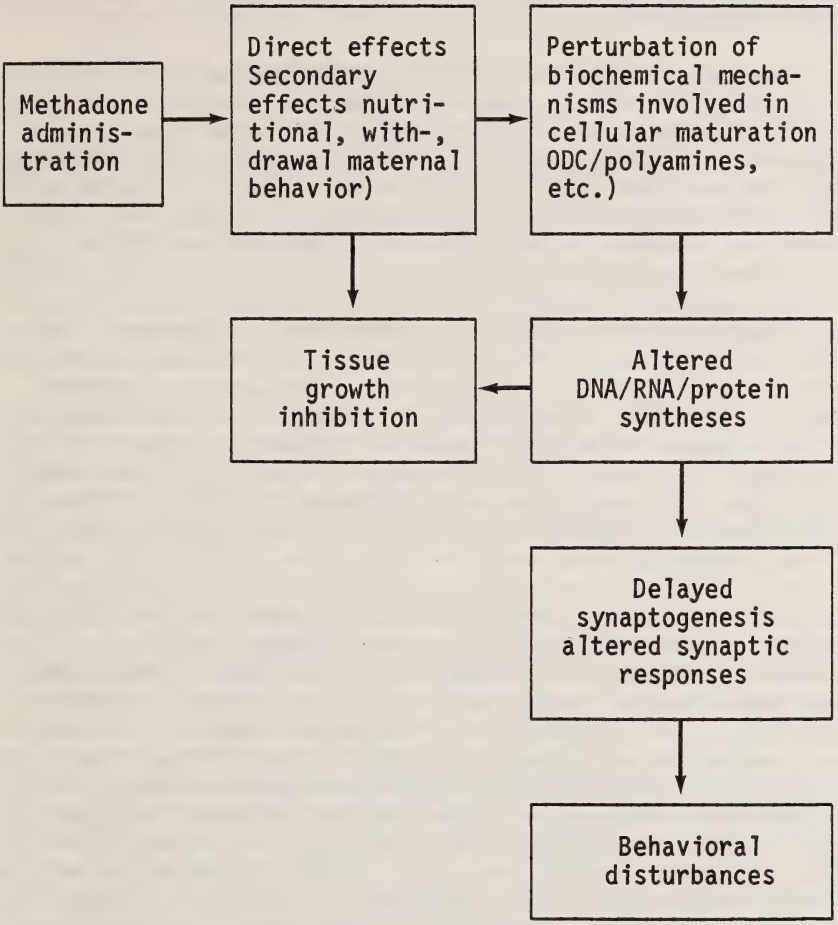
In this review of the pharmacology and behavioral aspects of preclinical research in the perinatal methadone field, Sparber has raised, in detail, one key issue: whether the animal models utilized by virtually every investigator are adequate reflections of human clinical experience with methadone maintenance. As he has pointed out, nearly all the animal research done on this problem was initiated with doses or injection regimens of methadone which produce growth retardation in the offspring along with some maternal or neonatal mortality. It is incontrovertible that secondary effects of such exposures, including nutritional shortfalls, maternal behavioral changes, endocrinological abnormalities, and episodic withdrawal may all participate in adverse morphological, biochemical, or behavioral outcomes. Sparber concludes that all such studies are therefore "futile" or "counterproductive," and offers his own results with another opiate (LAAM) as an example of how research must be conducted. Implicit in this line of argument is that the only object of animal research is to match as closely as possible the conditions of human perinatal methadone exposure, a point which, if valid, indicates that all other scientists in the field are purposelessly performing irrelevant research. This line of reasoning is clearly incorrect on several grounds.

First, human opiate exposures do not occur in the total absence of these secondary effects of the drug; in the discussion of Kreek's work on plasma steroid levels, it was indicated that a cortisol surge, consistent with onset of withdrawal, is prominent in between the daily doses of methadone in humans. Additionally, factors such as impaired growth and malnutrition are often clear-cut components of the perinatal opiate syndrome in humans, as reported by numerous investigators. All of these "epiphenomena" will be even more prominent if the pregnant addict is supplementing a methadone regimen with street drugs or if only street drug addiction is involved. The proper investigation of the consequences of perinatal methadone exposure thus requires that effects of the syndrome as a whole (direct effects plus secondary effects) be examined along with dissection of specific mechanisms as advocated by Sparber.

Secondly, it is absolutely futile to attempt to duplicate the conditions present in human addiction using an animal model for the simple reason that the developmental timetables of the species typically used (rat, mouse, chick) do not even remotely resemble that of the human. For example, the central nervous system of the rat is extremely immature at birth, and the period of most rapid synaptogenesis is in the second to third week of postnatal life (Coyle and Axelrod 1971, 1972; Slotkin et al. 1979). If maternal exposure is conducted in the manner typified by Sparber's studies, one cannot then examine the effects of such exposures on synaptic development, and instead a postnatal exposure is required. It is no wonder, then, that many investigations have found the most profound effects in the rat model with postnatal exposure (Butler and Schanberg 1975; Zagon and McLaughlin 1977a, b, 1978; McLaughlin et al. 1978; Anderson and Slotkin 1975; Slotkin et al. 1976, 1979).

The problem of disparate developmental patterns and timing is even further compounded when a nonmammalian species (chick) is used. Thus, two of the primary reasons that most investigators do not attempt to duplicate a perfect human maintenance schedule are that secondary effects are likely to occur in any perinatal opiate study (human or animal) and that animal models are inherently unlike humans because of the differences in the processes occurring during development.

As a consequence, the main purposes of preclinical animal studies in the pharmacological and behavioral areas have been oriented toward two goals: the identification of adverse developmental effects of the perinatal opiate syndrome, and the use of opiate administration as a perturbation tool to examine ongoing developmental processes. Progress has been notable in both these areas over the last decade, and has permitted at least a partial understanding of what sorts of developmental damage can occur and some of the causal factors which elicit the alterations. What is striking, despite the different routes of administration, dosage schedules, and age at which dosing is commenced, is the general uniformity of the conclusions reached by different investigators using basically dissimilar detection methods (behavioral, biochemical, in vivo, in vitro, etc.). As a major example, the sequence of events leading to altered behavioral states can be summarized in the following model:


Methadone administration
Direct effects Secondary effects nutritional, withdrawal maternal behavior)
Perturbation of biochemical mechanisms involved in cellular maturation ODC/polyamines, etc.)
Tissue growth inhibition
Altered DNA/RNA/protein syntheses
Delayed synaptogenesis altered synaptic responses
Behavioral disturbances

The assembly of such a sequence has required a prolonged period of work by several groups of investigators. Perturbations of the ornithine decarboxylase (ODC)/ polyamine system were first identified with morphine administration by Butler and Schanberg (1975) and were later extended to include perinatal methadone exposure (Slotkin et al. 1976, 1980; Seidler et al. 1981); this system regulates nucleic acid and protein syntheses during development and growth of tissues (Slotkin 1979; Russell 1980), and the effects of methadone on ODC are followed by impairment of nucleic acid and protein synthesis (Steele and Johannesson 1975; Hui et al. 1975; Peters 1977; Zagon and McLaughlin 1978), which leads to

the generalized inhibition of tissue development noted by many investigators.

In the brain, this impairment is expressed as a deficit in synaptogenesis of a variety of neurotransmitter systems followed by impaired synaptic responses to neurotransmitters (Lau et al. 1977; Slotkin et al. 1979; 1982; McGinty and Ford 1980; Seidler et al. 1981). Ultimately, such biochemical effects could produce the behavioral alterations associated with the perinatal opiate syndrome as reviewed by Sparber.

It should be noted that this scheme does not necessarily distinguish between the direct effects of methadone and its secondary actions as pointed out in Sparber's review, and in one sense, specificity or primary site of effect is not the most important question raised by these studies. If the final events are deleterious to function in offspring of addicted dams, then it is vital to identify what the defects are and the chain of events which leads to the alterations.

Be that as it may, several investigations do eliminate a number of secondary effects as contributors to this scheme. For example, McGinty and Ford (1980) showed that the impairment of synaptogenesis in the central nervous system is independent of maternal undernutrition; effects on development of catecholaminergic nerve terminals were readily detectable whether methadone exposed animals were compared to offspring of pair-fed dams or dams fed ad lib. These results have been confirmed and extended to the ODC system by Seidler et al. (1981). Similarly, various investigators have noted that the pattern of impairment of nucleic acid synthesis, organ growth, or even neurotransmitter development seen in offspring of methadone treated dams bears no relationship to that in similarly malnourished, drug-naive controls (Heggeness et al. 1970; Hsueh et al. 1976; Raye et al. 1977; Peters 1977; Zagon and McLaughlin 1977a, b, 1978, 1982), suggesting that methadone may impair growth directly. It should be noted that these studies have dealt with both the issues of maternal undernutrition as well as undernutrition in the offspring. Similarly, the types of defects of cellular development, neurochemical maturation, and growth associated with altered thyroid or adrenocortical status or with hypoxia are distinctly different from those seen with perinatal opiate exposure (Eayrs 1961, 1971; Schapiro 1968; Eranko and Eranko 1972; Balazs et al. 1971, 1975; Hamburgh et al. 1971; Nicholson and Altman

1972; Hedner 1978; Bohn and Lauder 1980; Lengvari et al. 1980; Lau and Slotkin 1980, 1981, 1982).

Finally, the most convincing demonstration that growth impairment and associated biochemical alterations are intimately associated with methadone itself has been obtained in tissue culture, where methadone alters ornithine decarboxylase and growth in much the same manner as it does in offspring exposed to the drug perinatally *in vivo* (Grode and Murray 1973; Willson et al. 1976; Vernadakis et al. 1981). It is difficult to see how "epiphenomena" such as withdrawal, maternal behavior, and hormonal status would operate to produce these effects in tissue culture systems.

These considerations aside, it is apparent that mechanisms operating in the perinatal opiate syndrome can best be approached by identification of overt adverse effects apparent in a "worst case" paradigm; once these effects are known, subsequent experiments can be done to typify whether the actions are a direct effect of methadone on the system or whether secondary actions predominate. Indeed, in criticizing this approach in his review, Sparber has used precisely this procedure to identify which secondary effects are operating to produce behavioral or biochemical alterations. There is nothing unique in such an approach to teratological or toxicological problems; the use of high doses is typical of initial attempts to isolate subtle as well as overt drug effects. It is essential, however, that dose-effect studies (Hutchings et al. 1976; Slotkin et al. 1980) be conducted to determine whether a threshold for perturbation of development exists and whether such thresholds are the same as that of growth inhibition or other easily determined parameters. In this regard, the effects of perinatal methadone exposure on brain ornithine decarboxylase have been shown to occur only at doses of methadone which affect brain growth (Slotkin et al. 1980), indicating that growth measurements can provide a reliable index of whether to expect subsequent developmental damage to the nervous system.

On the other hand, the same study showed that perturbations of cardiac biochemistry were observed even when growth was not suppressed, demonstrating that in some tissues, more subtle alterations can still occur even when doses of methadone are reduced to the point where birth weight and subsequent growth are within normal limits.

It is thus apparent that an understanding of how perinatal methadone exposure affects development requires at least two approaches to the problem: identification of the deleterious effects, which include sequelae related to secondary actions of methadone, and mechanistic studies in which selected secondary actions are examined to see if these are responsible for the developmental perturbation. There is clearly a need and requirement for both approaches if we are to understand the overall impact of perinatal opiate exposure on the individual.

A second major objective for which opiate administration during development has provided information has involved the use of opiate challenge to elucidate maturation of mechanisms related to endogenous opioids and their receptors. Kuhn and Schanberg (1981) utilized postnatal opiate administration to typify the time course of development of pituitary hormone secretory mechanisms, as have Chantry et al. (1982) in identifying development of sympatho-adrenal response capabilities. In studies of catecholaminergic neuron development, use has been made of the differential effects of opiates on central vs peripheral catecholamine turnover to elucidate the role of impulse flow in outgrowth of synaptic terminals (Slotkin et al. 1981). It should not be overlooked that the increasingly obvious role of enkephalins and opiate receptors in nervous system function will lead to further investigations in which fetal or neonatal opiate administration will serve as a tool in identification of specific developmental mechanisms. Current examples of this include studies of regulation of opiate receptor development in the central nervous system (Coyle and Pert 1976; Diaz et al. 1978; Tsang and Ng 1980) and the role of enkephalins and opiate receptors in mediating adrenomedullary responses to stress in neonates (Chantry et al. 1982).

Sparber's cautionary recommendations on the use of opiates as a developmental tool should not be disregarded; however, it is clear that there are a number of circumstances in which such uses can provide valid and important information. It must also be noted that <u>all</u> drugs given to a developing organism cause a spectrum of primary and secondary changes which can evoke subsequent alterations of development; there is nothing uniquely "confounding" about opiates in this regard, and a similar argument would lead to the conclusion that no studies should be done at all with <u>any</u> drug given during development.

In summary, clear-cut progress has been made in identification of developmental alterations caused by perinatal methadone exposure in animal models. Although separation of primary effects of drug exposure from secondary actions has not also proven feasible, there is every reason to expect that the mechanisms underlying the effects will be identified in ensuing work in the field. At this stage, substantial agreement has been reached among most investigators that behavioral alterations do occur and are related to fundamental deficits in neurochemistry, synaptogenesis, and synaptic function, and that at least some of the secondary effects of methadone can be ruled out as major participants in the deficits. It is of key importance that, despite differences in design of animal vs clinical studies, learning deficits and behavioral disturbances have been found in human offspring of addicted mothers (Ting et al. 1975; Wilson 1975; Wilson et al. 1979), just as one would expect from the preclinical investigations.

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CRITIQUE

Theodore J. Cicero, Ph.D.

Dr. Sparber's review succinctly summarizes the developmental aspects of pre- and perinatal methadone exposure in animals and points out some of the significant conceptual and theoretical problems which have plagued this field of study from its very inception. In addition, I believe his suggestions for future research directions are, for the most part, well-taken, although I have several to add.

I have a number of additional comments to make which I believe clarify, or expand upon, some of the points Dr. Sparber has made; moreover, there are several other points which I believe need to be made. As a point of departure from Dr. Sparber's comments, I have chosen not to focus specifically on particular studies for two reasons: first, he has adequately summarized most of the pertinent literature with the exception of endocrine studies, which I will touch upon; and second, the problems in this field, as I perceive them, are not restricted to one paper or the work of one group--rather, there seems to be a general pervasiveness of these problems.

I. Why Study the Developmental Aspects of Pre- and Perinatal Methadone Administration?

It seems rather unnecessary to pose this question in the context of a publication directed at the issue of the effects of methadone on developmental processes, since one would think that most workers already have a clear idea of why they are doing specific studies and what they expect to learn. Unfortunately, it is my contention that most, if not all, investigators cannot answer this question. It is true many workers profess to know what the objectives of their studies are, but then design experiments in such a way that these goals cannot be achieved. In either event, it seems clear to this reviewer that a great many "developmental pharmacologists" do not understand the true purposes of examining the pre- and perinatal effects of methadone and what are the strengths and limitations of their approach.

Obviously, there are two reasons to examine the developmental consequences of *in utero* or perinatal exposure to

methadone in animals: (a) as a model to examine pertinent clinical issues related to the use of methadone during pregnancy; and (b) as a specific pharmacological probe to selectively examine the behavioral, neurochemical, and structural aspects of development. It should be stressed that these are the only legitimate objectives for such endeavors, and all studies have to be judged solely on the basis of the extent to which they address one of these broad goals.

With respect to the development of an animal model for the use of methadone during pregnancy, I believe it can be confidently stated that there are few, if any, studies which have come even reasonably close to this objective. The reasons for this conclusion have been covered rather well in Dr. Sparber's critique. Briefly, most studies have employed paradigms in which gravid females are initiated on methadone dose regimens at various points in the gestation period, presumably to examine "critical" periods. The doses employed are usually very high and are generally selected to be the highest possible which are not lethal to a large percentage of embryos or fetuses. This is hardly analogous to the now judicious use of methadone in pregnant human females. If one wishes to develop a model of the human situation, it is imperative that studies be carried out in females exposed to opiates long before conception and then maintained on a low-dose regimen throughout the gestation period. Until the latter paradigm is utilized, it would be wise for investigators to stop introducing their studies with statements concerning the clinical relevance of their impending experiments. Their studies clearly are not relevant and such statements have already, perhaps erroneously, done great damage to the possible clinically efficacious use of methadone maintenance during pregnancy.

Of course, it is not necessary that one carry out developmental studies as a means of developing an animal model of human methadone usage. Rather, methadone could potentially serve as a useful probe to study the developmental process itself. The utility of such a pharmacological probe is limited, however, by two factors: first, that the drug has a specific, well defined pharmacological profile which would make any results easily interpretable; and second, that the doses employed do not introduce unwanted and confounding variables. Regrettably, all of the developmental studies known to this reviewer have not properly used methadone as a specific probe for the reasons outlined below.

As mentioned above, most investigators have deliberately (and often inadvertently) used barely sublethal doses of methadone which resulted in pronounced effects on the developmental parameter being examined. It is understandable that an investigator would wish to maximize his chances of observing a drug effect, but, under these experimental conditions, methadone loses its utility as a specific pharmacological probe. That is, all opiates have specific, naloxone-reversible effects at pharmacologically relevant doses, but when very high levels of the drugs are employed, many effects emerge which are not specific to opiate related compounds. Thus, the characteristic opiate pharmacological profile is lost, and the additional "drug" effects represent a significant source of confounding variables. As a result, the utility of methadone as a probe to study developmental processes has been seriously compromised in most studies carried out to date.

There are a number of nonspecific effects which can be ascribed to high-dose methadone administration, but without question the most serious problem is a reduction in food intake and malabsorption of important nutrients resulting in seriously undernourished animals. Since the effects of undernutrition on the development of the brain are well known (and are quite similar to those effects observed in many studies of methadone's pre- and perinatal effects), it is virtually impossible to draw meaningful conclusions about the specificity of methadone's disruptive effects on developmental processes when very high doses are employed. Although it would obviously be best to avoid these high dose regimens entirely, if they are employed, pair-fed controls must be utilized. Amazingly, this obvious control has been included in very few studies and, consequently, it is my view that the results of these poorly designed studies should be dismissed out of hand. (Hopefully, reviewers of manuscripts will consider this issue and help eliminate the seemingly endless pollution of the literature with meaningless results.) One critical caveat should be recognized, however, when pair-fed controls are utilized. Specifically, it is probable that the effects of a drug in a normal, healthy animal are very much different that those observed in an undernourished animal.

For example, it should not be surprising that a debilitated animal would display an increased sensitivity to further drug-induced insults introduced by methadone.

Thus, while a pair-fed control is essential, if poor nutrition is a problem in methadone treated animals, conclusions regarding specific effects of methadone on developmental processes should be viewed with considerable caution. The solution to this problem is really quite obvious: doses of methadone should be employed which do not produce these nonspecific effects in the first place.

An argument commonly advanced to counter the points raised above is that it may be that a large component of methadone's effects on development in the human is nonspecific toxicity. This argument is ridiculous and indicates that those promoting it have no appreciation whatever for why one does studies in animals, i.e., to tease apart what may be a very complex situation in the human. Moreover, if an investigator believes "toxicity" is the basis for methadone's adverse effects, then why study a drug with such a complex pharmacological profile? There are many ways to produce such toxic effects as undernutrition, for example, and these preparations would be preferable since they do not introduce the confounding variables of methadone's other actions! It seems to me that investigators can't have it both ways and must decide, as emphasized above, just what it is that they wish to study before they begin a large research program. It is clearly unacceptable to obtain the data first (in poorly designed and executed studies) and then try to explain the results in some fashion.

On the basis of the preceding discussion, it is apparent that most, if not all, investigators studying the effects of pre- and perinatal methadone exposure on development have not yet come to grips with the issue of what it is that they are trying to investigate. Once they determine if they are seeking an animal model of the human use of methadone or a means to selectively disrupt developmental processes, then they should design studies which would meet these objectives. Thus far, they have not.

II. Subtle Effects of Opiates

What is perhaps most surprising in a review of the effects of methadone on development is why high doses are employed in the first place. Many important effects of methadone occur at very small doses, and there seems to be little rationale in engaging in overkill. As a pertinent example, it has been found by a number of investigators that the endocrine system is exquisitely sensitive

to the opiates; the dose of opiates required to elevate growth hormone or prolactin or depress luteinizing hormone or testosterone is very low--generally 1/10th the ED_{50} for analgesia. This example was selected for two reasons: first, to illustrate that high doses of methadone are certainly not required to produce biologically significant effects; and second, to focus attention on opiate induced alterations in the endocrine system which could very well mediate the effects of these drugs on the development of the brain. Since the endocrine status of pregnant females profoundly affects the development of their offspring, and perinatal perturbations in endocrine homeostasis are also critical determinants of subsequent development, it is surprising that so little attention has been paid to these variables. Moreover, since these endocrine effects have been shown to occur at very low doses of methadone, which would not introduce the confounding variable discussed above, such studies could be of critical importance. Dr. Sparber's review only briefly and incompletely touches upon the endocrine effects of opiates and, unfortunately, space limitations do not permit me to provide a more complete review here. The interested reader is referred to several recent reviews which summarize this important information (Cicero 1980a,b).

From the preceding discussion, it seems apparent that high doses of methadone are certainly not required to examine the developmental aspects of the drug, since effects can and do occur at very low doses. Attempts to use low doses of methadone should be encouraged, since this paradigm could for the first time permit an ultimate assessment of whether methadone can be used as a selective probe to study developmental processes and, perhaps, simulate a model of clinically relevant drug usage.

As a final comment regarding the subtlety of opiate's effects, which has been obscured in the "sledge-hammer" approach used in most studies, it should be noted, as briefly touched upon by Dr. Sparber, that several investigators have observed long-term effects of relatively modest doses of opiates given sometime before conception on the subsequent development of offspring. Although Dr. Sparber mentions a few studies in females, there is an extremely interesting series of studies emerging from the laboratory of Dr. Gladys Friedler, Boston University School of Medicine, which demonstrate profound effects of paternal opiate administration, 1 week or more prior to mating with drug-naive females, on the development of

their offspring. Thus far, the following changes have been noted in adult male offspring of morphine treated fathers: endocrine disturbances, learning deficits, gross weight differences, and altered sensitivity to opiates (Friedler 1974; Friedler and Wurster-Hill 1974; Friedler et al. 1982). Of perhaps even greater significance, these effects appear to be produced by single injections of opiates and are transferred from one generation to the next (Friedler 1974; Friedler and Wurster-Hill 1974; Friedler et al. 1982)

These important preconceptual factors in both males and females have been virtually ignored by workers interested in the developmental aspects of methadone, and this situation should be rectified since these effects may be clinically relevant; indeed, they may be more important than the in utero or perinatal effects of methadone which have occupied the interests of so many workers (particularly considering the inappropriate way in which the latter studies have been carried out).

III. Has Anything New Emerged in the Last 10 Years?

Dr. Sparber states that little new information seems to have emerged since the original reports 10 years ago indicating that methadone was teratological. While I agree that most studies have merely further documented this phenomenon, I disagree with his basic conclusion that nothing new has emerged. The most significant development in my view is that, as investigators begin to appreciate the complexities of their studies, they have slowly begun to include appropriate controls in their experiments. This is laudible and long overdue, but regrettably a close inspection of the literature indicates that as doses are decreased, comparisons are made to pair-fed controls, etc., the effects of methadone on the behavioral, neurochemical, and ultrastructural development of the brain tend to be minimized. I'm afraid with more controls and appropriate models, we may well find that all of these initial results are invalid--at least with respect to specific effects of methadone on development. This is a new development, but one which is likely to be a bitter pill to swallow by many investigators and may return the whole field to the starting point once again. In my view, this is precisely what is needed.

IV. Future Directions

Dr. Sparber has provided some extremely useful suggestions for future research directions, and I will not reiterate those here. Rather, I would like to offer several of my own.

First, investigators must carefully keep in mind the general objectives of developmental studies and begin to design studies which will permit them to meet these goals.

Second, it is high time that the descriptive approach which has typified studies of the pre- and perinatal effects of methadone on development be supplemented with systematic studies of the mechanisms involved in these actions. As the first step, of course, it is necessary to reduce methadone dose regimens such that doses are employed at which the drug exerts specific and well defined effects. With this objective met, studies can be undertaken to determine which effects of the drug are most critically involved in the developmental parameter being examined. Although numerous opiate-specific actions of methadone could be involved, it is strongly urged that the role of opiate induced perturbations in endocrine function in the developmental effects of methadone be an area of highest research priority for the reasons stated above.

Third, the effects of paternal and maternal opiate administration prior to conception should also receive heavy emphasis.

Finally, using appropriate and clinically relevant doses of methadone, much more subtle, yet important, effects of methadone on developmental indices should be sought.

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CRITIQUE

Donald E. Hutchings, Ph.D.

Dr. Sparber's paper is certainly a provocative document. He raises several critical issues regarding the animal work that I find quite interesting, and welcome the opportunity for comment. I shall hasten to add at the outset, however, that I do not approach the document as a disinterested reader. Our laboratory has been carrying out animal research with methadone for nearly 10 years and some of Dr. Sparber's criticisms bear directly on our effort. However, while there are points of honest disagreement with Dr. Sparber, there are also areas of agreement. But because some readers of the document have objected, not without justification, to the occasional invective tone, I think what is needed most at this juncture is a bit more light and a little less heat. This I will attempt, both with dispassion and objectivity.

Sparber considers that "the most remarkable effect" to have been reported to be associated with methadone addiction of the human neonate is "the protracted and difficult-to-treat withdrawal syndrome." He then goes on to say that "few if any of the animal studies pay more than lip service to the possibility that perinatal abstinence may be an important determinant of the outcome of exposure to opiates during development." In support of this contention, he cites largely his own studies with LAAM using the chick embryo and rat which showed that naloxone induced withdrawal during late gestation increases mortality. I would summarize his argument as follows.

Exposure of an organism to one of the opiates produces tolerance and physical dependence and when the compound is discontinued, withdrawal or abstinence symptoms results. Sparber suggests "the possibility of fetal or neonatal withdrawal being responsible for some of the behavioral, neurochemical or endocrinological alteration. . ." seen in the offspring. In other words, sequelae are not produced by exposure of embryonic and fetal tissues to the compound as such but rather by abstinence--presumably, the biochemical concomitants that are produced when the compound leaves fetal or neonatal tissue. While Sparber does not elaborate, this hypothesis would predict that the occurrence of later sequelae in the offspring will covary with severity of abstinence; when withdrawal is severe, later offspring effects will

be severe whereas if abstinence can be attenuated or blocked, later effects will be either reduced or not appear.

In support of this hypothesis, Sparber cites his work (Lichtblau and Sparber 1981a), which showed that when pregnant dams are maintained on LAAM throughout pregnancy and then administered naloxone daily from day 15 until parturition in order to precipitate daily abstinence, these litters show a significantly lower birthweight and higher incidence of stillbirth compared with those exposed to LAAM alone. They argue that "in utero withdrawal, rather than opiates per se, may be responsible for at least some of the deleterious effects attributed to this class of drugs." On the other hand, these same workers (1981b) found a significant dose-related increase in postnatal mortality among litters exposed to LAAM throughout gestation. Neither the dams nor pups were administered naloxone and yet 74 percent of a 2.0 mg/kg litter and 22 percent of a 0.2 mg/kg litter died during the first postnatal week.

I mention this finding because Hutchings et al. (1980) found that litters from dams administered 5, 7.5, or 10 mg/kg of methadone during the last 2 weeks of gestation show virtually no mortality during the entire postnatal period. We presented evidence indicating that litters in the lowest dose-level group were undergoing abstinence. Compared with LAAM, methadone is a shorter acting opiate and, given that more rapid clearance is associated with more severe abstinence, our pups should have been undergoing more severe withdrawal compared with pups exposed to 0.2 mg/kg of LAAM. Yet our mortality rate was no greater than controls, while 22 percent of the LAAM-exposed pups died.

Sparber's abstinence hypothesis certainly has merit and deserves further study. The data offered in its support, however, bear only on birthweight and mortality, not neurobehavioral sequelae, and are derived from studies of abstinence precipitated by naloxone. Such effects are extraordinarily severe, making generalizations to effects on nonprecipitated abstinence of questionable validity. The sort of data that would be of interest would include studies of the effects of varying degrees of nonprecipitated abstinence as well as blocked withdrawal, possibly with the use of clonidine.

Before going on to other portions of the next section, I must say that though admittedly tempted, I will resist picking up the gauntlet in response to Sparber's statement that nothing new has appeared in the animal literature since 1975. My first contribution to this area appeared in 1976, so not to disagree is tantamount to a repudiation of my own effort. But instead, I refer the reader to a recent review (Hutchings, 1982) so he or she may judge what has been accomplished since 1975. To give the reader a hint, however, of Sparber's lapses in objectivity and comprehension of the literature, I will briefly cite one example which is typical of much to follow. He states that since 1975 "every subsequent study has utilized procedures which result in significant mortality, growth retardation, etc., even though the authors may continue to study the survivors. . ." Our laboratory specifically undertook a study of the cause of the maternal and offspring mortality associated with prenatal methadone exposure (Hutchings et al. 1980). To determine if the increments in our stepwise dosing regimen were too high to allow the dams to develop tolerance, these were reduced by half. Under these conditions, a dose-level regimen of 10 mg/kg that had previously produced a maternal mortality ranging from 23 to 45 percent produced no deaths among the dams. We also found no reduction in birthweight and went on to find behavioral effects in the offspring. While the work of our laboratory spanning some 5 years appears in Sparber's appendix, not once is it discussed or referenced in the text.

What follows by Sparber is a broadside assault on the preclinical literature. But with the exception of the work by Zagon and coworkers, these reports are largely relegated to an appendix and never discussed for the stated reason that they are "typical in most respects" of Zagon's work. So having neatly set aside and dismissed these mere clones, so to speak, of Zagon, Sparber proceeds with his critique.

In yet another of his sweeping indictments, he states that "nobody has attempted to truly replicate in animals a model which closely parallels the clinical exposure of pregnant women and their fetuses. . . ." Unfortunately, there has been little if any discussion in the animal literature of what constitutes an adequate model of methadone exposure. Several points are worth making here.

First, to refer to the animal work as "preclinical" is a misnomer; the bulk of this research appeared after methadone had become a widely accepted and standard treatment for heroin addiction. In this regard, methadone is unique in that the animal research was, in fact, post-clinical, a circumstance which allowed the comparison of animal results with the clinical findings. Second, when the animal work began in the mid-1970s, the clinical literature was extremely controversial, with most papers arguing about the differential effects of methadone and heroin, particularly with respect to neonatal withdrawal, birthweight, and mortality.

For our work, we specifically avoided a mere replication of the clinical model in order to address particular questions from a basic research perspective. Because of the findings of Friedler and Cochin (1972) of offspring effects following maternal exposure prior to pregnancy, we initiated treatment during pregnancy. And since there were no good clinical or animal data regarding possible toxic effects of methadone on the blastocyst, we initiated treatment on gestation day 8 following implantation. This procedure permitted us to conclude that observed effects were produced specifically by exposing the embryo and fetus, and did not result from pregestational exposure of the dam of toxic effects on the blastocyst. Following this same sort of rationale, Middaugh and Simpson (1980) administered methadone to the mouse only on the last week of gestation and replicated a behavioral effect that we had reported in the rat (Hutchings et al. 1979). Their finding suggests that at least some of the neurobehavioral sequelae of methadone exposure are produced by exposure during late gestation. I therefore stand in disagreement with Sparber's contention that we should merely replicate the clinical dosing schedule. I feel that several schedules provide answers to important basic questions of mechanism of action that ultimately converge on the issue of risk assessment.

Sparber attempts to make a case for not dosing pregnant dams on a mg/kg bodyweight basis. His rationale appears to be his success with such a procedure. I think it is a mistake, however, to approach this complex problem with an either/or attitude. Let's see the results of using both dosing techniques to determine the relative advantages. I would suspect, though, that given the large differences in the number of implanted embryos and,

therefore, large variations in maternal weight gain, dosing dams on the basis of pre-pregnancy weight would necessarily produce large differences in blood levels of the drug, particularly by the third week of gestation. As in the case when choosing one technique over another, generally each has advantages and disadvantages, and making one choice invariably represents some sort of compromise.

Sparber states that the ". . .plasma halflife of methadone administered to rats, even orally, (is) so short (about 1 to 5 hours) that injecting rats once per day with 5 mg/kg is probably producing acute toxicity, followed by episodic withdrawal sometime before the next dose. We have shown that this is so with morphine injected every 12 hours . . ., and no reason exists to believe the situation differs in rats dependent upon and injected daily with methadone."

I am not a pharmacologist but I would guess that there is some tacit rule warning against the glib generalization from one compound to another. Throughout, Sparber does this with impunity, repeatedly comparing methadone, LAAM, and morphine. This is not so vexing when he's merely guessing for lack of data, but when he ignores well known differences, it's troubling.

For example, as Sparber must be aware, there are fundamental differences between morphine and methadone. Morphine appears not to accumulate in tissue, and 24 hours after the last dose, as Sparber suggests, tissue concentrations are indeed low. But such is not the case with methadone. It appears to firmly bind to protein, including brain, and as our data suggested (Hutchings et al. 1979), after repeated administration it gradually accumulates in tissue. Moreover when administration is discontinued, low plasma concentrations are maintained by slow release from binding sites.

But what about plasma levels of methadone? This is a point that Sparber repeatedly makes both in this document and his LAAM publications--that the plasma halflife of methadone is so short that animals must be undergoing daily withdrawal. To support his contention, he cites the study of Misra et al. (1973), but what is puzzling is that he discusses those findings that support his argument and ignores others that do not. These workers found that the plasma halflife of methadone in the rat varies as a function of the route of administration and whether

or not they are tolerant. Oral administration produced plasma levels about 1/25 of that found for the s.c. route, and rate of disappearance from plasma was faster in tolerant compared with nontolerant rats--the shortest halflife was 1.4 hours for tolerant animals administered by the oral route and the longest was 8 hours of nontolerant animals by the same route. The interesting omission in Sparber's discussion is what Misra and coworkers found for brain, observations that I would consider to be at least as important as plasma, if not more so, for discussing withdrawal. They found that regardless of the route of administration, "measurable quantities of drug persisted in brain and other tissues up to three weeks or longer, even though no measurable amounts of drug were present in plasma after 24 hours."

More directly to this point is our observation that following prenatal administration, methadone in offspring brain is equal to maternal brain on the day of birth and declines to about 22 percent during the first 5 days after birth. And similar to Misra's findings, we found the drug to persist in both offspring brain and liver until 30 days of age (Levitt et al. 1982). Indeed, we suggest that the withdrawal-like behavioral effects that we found during the third postnatal week (Hutchings et al. 1979) may result from the persistence of methadone in tissue. Further study will be required to verify this but our speculation is based on results with methadone and is a bit more circumspect than Sparber's based on LAAM.

The remainder of the document largely is a detailed criticism of the work of Zagon. While I have addressed some of these issues, I don't think it appropriate for me to defend Zagon, and feel that he should be afforded that opportunity. I would agree with Sparber, however, that for studies to be as relevant as possible to the clinical problem, it is desirable to use the oral route of administration. Furthermore, I feel strongly that every experimental report should include a complete description of morbidity, mortality, and birthweight regardless of how many reports from the same laboratory using the same procedures have been previously published. These tend to show considerable variation over time, with some effects periodically appearing and disappearing. They may occur with changes in staff, husbandry conditions, animal and drug supplier, and the like, but more often than not are inexplicable.

Finally, knowledge can be enhanced and enriched in an atmosphere that encourages forthright exchange of differences in interpretation and approach. But when language and tone become excessively provocative, one is apt to lose the target for the smoke. As I said earlier, what is needed now is a bit more light and a lot less heat.

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CRITIQUE

Ian S. Zagon, Ph.D.

In reading Dr. Sparber's assessment of the preclinical literature regarding the effects of methadone on offspring and users, one is reminded of the problems common to many reviews by individuals working outside of their subject area. A less than complete knowledge of a scientific area may lead to omission, dismissal, and even misinterpretation of important facts and details. In point of fact, examination of the reference list accompanying Dr. Sparber's review reveals that he has not published in the field of methadone and perinatal development. Indeed, Dr. Sparber apparently has not been the senior author of any peer-reviewed report on opiates and development.

In this paper I would like to address some of the salient topics on methadone and development that seem to trouble Dr. Sparber. Understandably, since my work has been singled out as "typical" of the field, I have chosen to focus on the research in my laboratory. In order to be as brief as possible, I have chosen the following topics to discuss: (a) drug protocol, (b) analgesia and enhanced sensitivity, (c) behavior, (d) nutrition, and (e) parallels between laboratory and clinical studies. For a more complete source of information the reader can refer to our article entitled, "Opiates, endorphins and the developing organism: A comprehensive bibliography" (Zagon et al. 1982).

Drug Protocol

Although one might expect that the effects of methadone would be closely related to its level in plasma, this is not the case. The absence of drug in the plasma does not preclude the presence of drug in body compartments, explaining why drugs having very short plasma halflives may possess prolonged action. The presence of even small amounts of drug in an area (e.g., brain) essential to drug response is of utmost importance. Perhaps the best example of this concerns endorphin activity in which only nano and picogram quantities are necessary to bind with opiate receptors in order to effect a response. In regard to methadone, this drug has been reported to have

a halflife in rodents ranging from a few hours (Misra et al. 1973) to over 24 hours (Ziring et al. 1981). It does appear that plasma concentrations of methadone have no direct correlation with the rate of metabolism or with brain concentrations of this drug (Liu and Wang 1975). In fact, methadone is known to bind firmly to tissue proteins (Sung et al. 1953) and to accumulate in body tissues (Dole and Kreek 1973; Misra et al. 1973), and methadone has been reported to persist in several organs including the brain for up to 10 weeks (Harte et al. 1976). It is also known that immature animals accumulate much larger amounts of methadone than adults (Peters et al. 1972; Shah et al. 1976; Shah and Donald 1979). In particular, the brains of fetal (Peters et al. 1972) and preweaning (Shah and Donald 1979) rats have high concentrations of methadone following acute injections, presumably because developing animals have an increased permeability due to the gradual formation of the blood-brain barrier postnatally. I might add that immature organisms also may not be able to cope with drugs as well as adults, and fetal storage and delayed metabolism and/or excretion could produce pharmacological effects that are even more pronounced than in adults (e.g., Kandall 1977).

With these facts in mind, we have chosen a drug dosage (5 mg/kg), route of administration (intraperitoneal (i.p.)), and schedule of injection (daily) that are based in large part on the work of Peters and colleagues (Buchenauer et al. 1974; Peters 1975, 1977, 1978; Peters et al. 1972). The maternal dosage of methadone was above the i.p. threshold for analgesic action in rats (1 mg/kg; Chen 1951) but well below the LD_{50} of 23 mg/kg (Barnes and Eltherington 1966). We have found that this is the maximal dosage which does not produce a high maternal mortality (greater than 5 percent), decreases in litter size, increases in the number of stillborns, or significant increases in infant mortality for pups maintained on methadone after birth. In our protocol, as well as that of many others, drug dosage is adjusted for body weight. This is predicated on the basis of dosage/volume distribution. Furthermore, such procedures serve to control the pharmacological regimen in order to provide meaningful data for within or between-group comparisons. I might add that in the clinical setting, dosage adjustments for volume of distribution must also be considered. Rementeria and Lotongkhum (1977) suggest that an increase in methadone dosage during later stages of pregnancy may need to be considered in order to compensate for the methadone utilized by the rapidly growing

fetus. Furthermore, failure to adjust the dosage near term not only can lead to increased drug craving, but also to fetal distress (e.g., Zuspan et al. 1975). Insofar as the i.p. route of drug administration is concerned, precautions (Peters 1975; Peters et al. 1972) were taken to insure i.p. rather than intrafetal or intrauterine deposition, and both in situ and histological examinations of the anterior abdominal wall revealed no signs of peritoneal inflammation or pathological areas of scar tissue. Moreover, saline injected mothers were used consistently to control for factors (e.g., stress, fluid in the abdominal cavity) introduced by this route of administration. In order to establish a pattern of drug exposure prior to conception, we have designed our injection schedule to begin 5 days before mating; typically, this provides a period of 1 or 2 weeks of methadone treatment before conception. Our results show that, by the second week, animals demonstrate tolerance to the respiratory depressive action of methadone (White and Zagon 1979), as well as to the subdued appearance following initial methadone injections. In addition, challenges with naloxone by the second week of the schedule produce symptoms of abstinence, indicating physical dependence (Zagon and McLaughlin, in preparation). Observations of the animals over a 24-hour period reveal no signs of episodic opioid withdrawal. Moreover, our dosage, route, and schedule of drug administration resulted in infant rats that were physically dependent on methadone. This was evident because pups withdrawn from methadone exposed mothers experienced abstinence symptoms that could lead to neonatal mortality. It should be noted that these observations have a clinical parallel; 60-90 percent of the infants of mothers with a recent history of narcotic abuse experience the withdrawal syndrome (Blinick et al. 1976; NIDA 1979; Perlmutter 1974) and, if left untreated, these infants may convulse and die. It is also interesting that although Dr. Sparber finds fault with methodology that records neonatal morbidity and mortality, the presence of neonatal withdrawal is necessary to document physical dependence. I might also point out that the inextricable link between neonatal mortality, withdrawal, and physical dependence plays a part in Dr. Sparber's studies as well. Thus, although Dr. Sparber advocates using a protocol that minimizes neonatal mortality, he has reported significant infant mortality when LAAM is administered to pregnant rats in very low but physically dependent dosages (Lichtblau and Sparber 1981). Finally, as a general comment, it should be recognized that in cases where neo-

natal mortality does exist, the number and magnitude of alterations are minimized because the data reflect only those animals surviving drug withdrawal.

Analgesia and Enhanced Sensitivity

A particularly troublesome area for Dr. Sparber appears to reside in our findings that rats perinatally exposed to methadone have an enhanced sensitivity to methadone exposure later in life. In his critique, Dr. Sparber infers that our techniques for evaluating analgesia may have obfuscated our results. However, the methodology employed--the hot-plate test--has been a standard pharmacological technique since the 1940s (e.g., Woolfe and MacDonald 1944), and had been successfully utilized to evaluate analgesic activity of narcotic compounds. The details of temperature and duration of exposure have been carefully investigated in order to maximize thermal sensitivity and to avoid tissue damage, even after repeated testing. Moreover, the number of investigations using this technique to study opiate action in young animals is considerable (e.g., O'Callaghan and Holtzman 1976, 1977; Johannesson and Becker 1972, 1973; Huidobro et al. 1976; Huidobro and Huidobro 1973).

It is interesting to note that our results showing enhanced sensitivity to methadone injections in animals perinatally exposed to methadone differs from earlier studies in which tolerance to morphine injection was observed in animals prenatally or postnatally subjected to morphine. However, a paper by Kirby et al. (1982) found that the offspring of animals prenatally exposed to 5 mg/kg morphine four times daily were hypersensitive to the analgesic action of morphine as young adults, but rats exposed to the same daily dosage given in only two injections displayed an analgesia similar to controls after subsequent morphine injections. The authors suggest that the differences between their study and those performed earlier reside in the schedule of morphine administration, with continual presence of morphine in the fetal plasma and nervous system responsible for the enhanced sensitivity later in life. There is an obvious parallel between the effect of the continual presence of morphine in the fetus (and neonate) found by Kirby and the enhanced sensitivity with methadone that we have observed.

Behavior

Several years ago, we (Zagon and McLaughlin 1978a) examined the effects of perinatal methadone exposure on behavioral ontogeny. By utilizing conventional and well documented techniques in behavioral research (Almli and Fisher 1977; Gard et al. 1967; Fox 1964; Blanck et al. 1967), we found that the timetable of behavioral maturation was often delayed in methadone exposed pups in comparison to control rats. In his review, Dr. Sparber infers that stress and handling during our testing procedure produced confounding results. However, Dr. Sparber fails to recognize that control animals also were tested by the same methodology and served for comparison. Moreover, Dr. Sparber cites literature on early experiences of animals to support his contentions. In fact, close inspection of this literature (Newton and Levine 1968; Levine 1957, 1962; Weininger 1956) shows that stress and handling early in life accelerates behavioral and somatic development; these results are antithetical to those found with opiate exposure.

Nutrition

Since opiates are known to affect the gastrointestinal tract (Burks 1976; Jaffe and Martin 1980), it has come to the attention of Dr. Sparber that undernutrition could account for the disruption in growth and development related to opiate treatment. There is considerable literature from laboratory and clinical studies (Naeye et al. 1973; Ford and Rhines 1979; Seidler et al. 1982; White et al. 1978; McLaughlin and Zagon 1980; McLaughlin et al. 1978; Zagon and McLaughlin 1977a, 1977b, 1978a, 1978b) indicating that maternal undernutrition does not appear to be the etiological basis for opiate related problems. In our laboratory, we found that food and water consumption in chronically treated mothers was not significantly reduced from control levels (White et al. 1978). Drug-treated litters were noted to suckle frequently and to have milk in their stomachs as often as controls (Zagon and McLaughlin 1977b). In addition, the significant decreases in litter size and birth weight that are often associated with mothers given restricted diets have not been observed with methadone treated females (Zagon and McLaughlin 1977b). Although cumulative undernutrition during gestation and lactation is known to be more detrimental than undernutrition during either gestation or lactation, animals exposed to methadone during gestation

and lactation do not demonstrate a cumulative response, but rather these pups often exhibit the fewest alterations (e.g., Zagon and McLaughlin 1977a, 1978a, 1978b). Moreover, the ratios of brain weight to body weight indicate that the brains of methadone treated pups were not "spared" as in the case of undernourished animals (Dobbing and Smart 1973), but appeared to be a sensitive target to the actions of methadone (Zagon and McLaughlin 1978b, 1977a). Finally, the changes in organ weights as a result of perinatal methadone exposure (McLaughlin and Zagon 1980; McLaughlin et al. 1978), as well as the constellation of behavioral and neurochemical changes recorded in these animals (Zagon and McLaughlin 1978a, 1978b; Zagon et al. 1979a, 1979b; Seidler et al. 1982), are not compatible with those occurring with undernutrition.

Dr. Sparber raises the question of whether undernutrition during the postnatal period rather than prenatal undernutrition may be an important factor in opiate studies. Recently, we (Zagon and McLaughlin 1982) have published a paper that addresses this issue. In our study, we directly compared the effects of postnatal exposure to methadone in animals raised in standard size litters of eight pups/mother to that of postnatal undernutrition in animals raised in litters of 18 pups/mother. The differences between these two treatments were striking. As anticipated from previous reports, 21-day-old undernourished rats weighed about half that of controls, but the undernourished rats had brain weight deficits of only 12 percent; the brain-body weight ratios of these animals were considerably elevated over control levels. In contrast, the methadone exposed pups had body weight deficits of only 19 percent, but brain weight deficits of 32 percent. Moreover, the methadone treated rats had more severe deficits in the weight and total DNA content of the brain and cerebellum, as well as brain DNA concentration, than undernourished animals. Further evidence that the growth inhibiting properties of methadone are not due to reduced caloric intake was garnered by the inclusion of groups of rats subjected to postnatal methadone exposure and undernutrition (control pups cross fostered at birth to a mother receiving methadone and raised in litters of 18 pups/mother). Although we expected these animals to show the greatest changes in body weight and brain neurochemistry, deficiencies of smaller magnitude than those occurring with methadone alone were often recorded. This "protection" afforded by combined treatment may have been effected by the reduced

milk consumption of the methadone-undernourished pups, thereby lowering their methadone intake, and hence reducing the drug related disturbances.

Parallels between Laboratory and Clinical Studies

Dr. Sparber's review overlooks perhaps the most important question of all. Are there parallels between laboratory and clinical findings? A positive answer to this question would (a) provide affirmation for the basic biological actions of opiates, (b) support the use of animal studies to investigate the mechanisms of opiate action, and (c) endorse the utilization of laboratory systems as prognosticators of impending clinical problems, as well as for the exploration and evaluation of therapeutic protocols. Although clinical studies are often replete with confounding variables that usually concern the mother (e.g., poor diet, alcohol and polydrug abuse), and despite the difficulties of extrapolating laboratory results to the human situation, a number of striking parallels between clinical and laboratory findings do exist. Neonates are passively addicted to opiates and experience drug withdrawal, exhibiting a high rate of morbidity and mortality if not given supportive therapy. Opiate exposed infants may undergo a subacute or protracted phase of withdrawal that could last for months. Infants and children exposed to methadone or heroin are less alert than control children, have poor attention spans, and have problems in visual orientation and motor coordination. In early life, children maternally exposed to opiates suffer sleep disturbances, display temper outbursts, impulsiveness, aggressiveness, and hyperactivity, may exhibit retardation in walking and speech development, and experience difficulties in learning and perception. Opiate exposed children are lighter in weight and smaller in stature than control children, and often tend to have subnormal head circumference measurements. Moreover, neuropathological studies on opiate exposed infants suggest abnormalities in the developing nervous system (Finnegan 1979; Wilson et al. 1973, 1979, 1981; Wilson 1975; Ramer and Lodge 1975; Lodge et al. 1975; Ting et al. 1975; Rosen and Johnson 1982).

In summary, a dramatic increase in the use of narcotics has occurred in the last 15 to 20 years, particularly among young women. Needless to say, a great deal of concern has recently been expressed as to the short- and

long-term consequences of perinatal narcotic exposure on the infant, child, and adult (NIDA 1977, 1979; Blinick et al. 1976; Rementeria 1977). Investigations in the laboratory have provided exciting new information as to the action and mechanisms regarding opiates and the developing organism. These laboratory findings also bear a rather dramatic correlation with the clinical situation, and continued research on both frontiers is urgently needed. Moreover, with the discovery of the endogenous opiates and their ligands, the opiate receptors, research activities with exogenous opiates will have even greater clinical and laboratory significance in unraveling the relationships of the endorphins to normal and abnormal growth and development.

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DISCUSSION SUMMARY OF CHAPTERS 2 AND 3

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Participants discussed the extent to which the findings in animals such as rats can be validly extrapolated to humans, attempted to determine what conclusions can be reached at present, and identified areas of high priority for further research.

Considerable, and sometimes heated, debate centered on the appropriateness of existing preclinical studies for exploring the perinatal and developmental effects of methadone. It was noted that in rats methadone has a very short halflife. Furthermore, daily doses of methadone as used in existing studies with rats have not been demonstrated to induce or maintain dependence. Some participants expressed the view that this existing animal model is less than representative of methadone maintenance in humans. Thus extrapolating the results of these studies to humans is difficult. However, members of the group recognized that, in biomedical studies in which large numbers of animals are needed to obtain statistically significant results, only small animals are practical to use.

The participants attempted to reach consensus on those conclusions that can be drawn in spite of the limitations discussed. Dr. Blake stated that methadone and other opioids have little or no gross morphological teratogenic potential, and the others present appeared to agree. Participants called for continued study of the possible chromosomal effects of methadone; one member of the group suggested performing a rigorous trial designed so that the use of street drugs would not confound the findings, and another proposed extending Falek's work to include more individuals. The group also agreed that the effects of perinatal methadone withdrawal require additional investigation. Also, it was recommended that the relationships of dose and response be established, and that more subtle measures of drug dependence be developed in rodents.

CHAPTER 4. CLINICAL PERINATAL AND DEVELOPMENT EFFECTS OF METHADONE

Loretta P. Finnegan, M.D.

INTRODUCTION

For centuries, women in general, and pregnant women in particular, have been exposed to psychoactive agents. During the last decade, clinical studies have become sophisticated enough to obtain pertinent data about the effects of these agents on pregnancy, the fetus, the neonate, and the child. In addition, the management of pregnancy complicated by opiate dependence has become a new area of medical specialization with the result that appropriate care has markedly decreased morbidity and mortality in both the pregnant woman and her child.

This chapter describes the clinical/perinatal and developmental effects of opiates, with specific attention to the effects of methadone. It discusses pharmacological aspects of perinatal narcotic use, the medical and psychosocial hazards of narcotic addiction in pregnancy, morbidity and mortality in infants born to heroin addicted and methadone maintained women, and clinical facets of neonatal narcotic abstinence. Most importantly, it addresses behavioral, developmental, and neurological evaluations in the neonatal period and infancy in relationship to prenatal narcotic use. The data reported herein are obtained from the literature and studies done by the author during the past decade.

PHARMACOLOGICAL ASPECTS OF PERINATAL NARCOTIC USE

Morphine is the major metabolite of heroin and methadone. Both heroin and methadone readily cross the placenta, and methadone has been identified and measured in amniotic fluid, cord blood, and neonatal urine (Blinick et al. 1975; Peters et al. 1972; Sanner and Woods 1965; Yeh and Woods 1970). Metabolism of narcotics may be altered during pregnancy by the effects of the hormonal milieu on drug metabolism in general. Very little is known about the effects of this altered hormonal state of pregnancy on drug metabolism in the human female, although in both

animal and in vitro studies it has been shown that estrogens may inhibit microsomal enzyme metabolism of several drugs, including narcotics, and that growth hormone, which is elevated during pregnancy, may also alter activity of microsomal drug metabolizing enzymes (Axelrod 1956; Neale and Parke 1973; Peters 1973). The role of the human placenta and human fetal liver in narcotic metabolism in vivo remains obscure. Similarly, the effects of other drugs, used or abused, during pregnancy, on narcotic metabolism are unknown.

Methadone is widely distributed throughout the body after oral ingestion, so that less than 6 percent is in the total blood volume at the time of peak plasma levels (Inturrisi and Verebely 1972; Kreek 1973; Sullivan and Blake 1972). It is metabolized primarily by the liver and excreted both as unchanged methadone and a variety of metabolites in urine and in feces (Inturrisi and Verebely 1972; Kreek 1973; Kreek et al. 1977; Kreek et al. 1976; Sullivan and Blake 1972). There is extensive nonspecific tissue binding of methadone, which creates reservoirs that can release unchanged methadone into the blood, thus contributing to its long duration of action (Dole and Kreek 1973). After ingestion of a maintenance dose of methadone in patients with no polydrug abuse, peak plasma levels occur between 2 and 6 hours after the oral dose, and plasma concentrations rarely exceed 1 μg/ml. Lower sustained plasma concentrations are present during the remainder of the 24-hour period (Kreek 1973).

Plasma levels of pregnant methadone maintained patients have been determined at the time of labor and delivery in 37 patients included in two studies (Kreek et al. 1972) and on repeated occasions during late pregnancy in a single patient in one study (Blinick et al. 1975; Kreek et al. 1974; Rosen and Pippenger 1975, 1976). The mean dose of methadone at the time of delivery in one study was approximately 80 mg/day and in a second study approximately 35 mg/day (Blinick et al. 1975; Rosen and Pippenger 1975, 1976). Blood was drawn at the time of delivery, with no fixed or documented relationship to time of last dose of methadone. In the first study, the random mean plasma level of methadone was 0.18 ± 0.3 μg/ml and in the second 0.16 ± 0.04 μg/ml. Pronounced interindividual variation in methadone disposition and resultant plasma levels, and possible differences in analytical techniques used may account for the similar plasma levels in patients with vastly different mean daily doses of methadone. In the study of one patient in whom

determinations of sequential plasma levels of methadone following an oral dose of methadone were carried out twice during pregnancy and three times during the post-partum period, it appeared that the plasma levels were somewhat lower after a given dose during pregnancy than following delivery, suggesting that there may be increases in fluid-space or tissue reservoirs for storing methadone or altered drug metabolism during late pregnancy (Kreek et al. 1974).

Amniotic fluid and cord blood levels of methadone have been measured in two sets of studies, sampling one and 18 patients, respectively, studied at the time of amniocentesis in mid-pregnancy or at the time of delivery (Blinick et al. 1974; Blinick et al. 1975; Kreek et al. 1974). In the first study, the presence of the two major N-demethylated metabolites of methadone (pyrrolidine and pyrroline) was identified in amniotic fluid along with unchanged methadone. The concentrations of methadone in amniotic fluid were significant (0.66 μg/ml) at the time when the cord blood levels were below the lower limits of detection (0.01 μg/ml) following a dose reduction from 110 mg to 9 mg/day over 37 days (Kreek et al. 1974). In the second set of studies, the concentrations of methadone in amniotic fluid ranged from 0.07 to 0.45 μg/ml in patients maintained on 30 to 100 mg of methadone/day (Blinick et al. 1974). In patients studied at the time of delivery, the mean ratio of amniotic fluid to maternal plasma levels of methadone was 0.73, and the mean ratio of cord blood to maternal plasma levels of methadone was 0.57 (Blinick et al. 1975). A similar ratio of cord blood to maternal plasma methadone levels of .50 at delivery was reported by Rosen and Pippenger (1975).

EFFECTS OF NARCOTIC ABUSE ON PREGNANCY

Opiate dependence in pregnancy is overwhelming not only to the physical condition of the woman but also to that of the fetus and eventually the newborn. The vast majority of these women neglect general health care and therefore are predisposed to a host of obstetrical and medical complications affecting their own and their fetus' well-being. Obstetrical complications associated with heroin addiction include: abortion, abruptio placentae, amnionitis, breach presentation, increased need for Caesarean section, chorioamnionitis, eclampsia, intrauterine death,

gestational diabetes, placental insufficiency, postpartum hemorrhage, preeclampsia, premature labor, premature rupture of membranes, and septic thrombophlebitis. About 10 to 15 percent of drug dependent women have toxemia of pregnancy, and nearly 50 percent of women who are heroin dependent and have no prenatal care deliver prematurely. The infant born to the drug dependent mother not only is born early but also weighs less than normal infants of the same gestational age (Connaughton et al. 1977).

Because of the lack of quality control in street drugs, the pregnant woman is likely to experience repeated episodes of withdrawal and overdose. Maternal narcotic withdrawal has been associated with the occurrence of stillbirth. Severe withdrawal is associated with increased muscular activity, which increases the metabolic rate and oxygen consumption in the pregnant woman. During maternal withdrawal, fetal activity also increases, and the oxygen needs of the fetus can be assumed to increase. Thus, the oxygen reserve in the intervillous space of the placenta may be unable to supply the extra oxygen needed by the fetus. Also, during labor, contractions compromise the blood flow through the uterus and consequently diminish the oxygen reserve in the intervillous space. The longer and stronger the contractions, the more compromised is the circulation through the uterus. If labor coincides with abstinence symptoms in the mother, the increased oxygen needs of the withdrawing fetus would occur during a period of variable uterine blood flow. The result may be fetal hypoxia and possibly death. Furthermore, as the fetus grows older, its metabolic rate and oxygen consumption increase; therefore a pregnant woman undergoing severe abstinence symptoms late in pregnancy would be less likely to supply the withdrawing fetus the oxygen it needs than would an addict in the first trimester (Rementeria and Nunag 1973).

Naeye et al. (1973), who studied other fetal complications of maternal heroin addiction, found that nearly 60 percent of the mothers, or their newborn infants, showed evidence of acute infection. Most of the infected mothers delivered prematurely, whereas the others delivered at term. The placentas of the heroin exposed infants commonly showed meconium histiocytosis, suggesting episodes of fetal distress, perhaps associated with hypoxia during heroin withdrawal. In addition, the infants born to these heroin addicts were, as a group, small for gestational age, with all of their organs affected. Maternal undernutrition was not sufficient to explain this retardation of fetal growth. This investigator suggested

that periodic episodes of heroin withdrawal during pregnancy might restrict fetal growth by reducing uterine or placental blood flow. However, it is unlikely that a uterine or placental disorder was responsible, since the organ and cellular growth pattern associated with fetal growth retardation in uteroplacental disorders differs from that observed in the offspring of heroin addicts. Specifically, in nonaddicted women, undernutrition restricts both the size and the number of cells in many organs during the last trimester; the adrenal glands, liver, and adipose tissue are affected more than other organs. However, the smallness of many of these organs in infants exposed to heroin in the third trimester resulted mainly from an abnormally low number of cells. Growth retardation of the addicted fetuses was still apparent even when maternal nutrition was taken into account. It thus seems likely that heroin directly affects antenatal growth (Naeye 1965; Gruenwald 1963).

Using ultrasound, Wapner et al. (1982) studied throughout pregnancy the growth of 99 fetuses passively exposed to methadone, heroin, or pentazocine. Total intrauterine volume, biparietal diameter, head circumference, and abdominal circumference were measured. All total intrauterine volumes and biparietal diameters of the 86 appropriate-for-gestational-age infants were within normal range. Low birth weight occurred in 21 percent of the infants (8 percent were premature and 13 percent small for gestational age); total intrauterine volumes were less than expected in 11. Scans of the 13 infants who were small for gestational age showed biparietal diameters below the mean for gestational age. The ratios of head circumference to abdominal circumference fell within the normal range.

Although pentazocine users constituted only 9 percent of the patients studied, their infants represented 54 percent of those who were small for gestational age (Wapner et al. 1982). These data suggest that early-onset symmetrical intrauterine growth retardation is observed in the fetuses of drug dependent women and furthermore that pentazocine has a high potential for causing small-for-gestational-age infants through a direct, rather than an environmental, effect.

In drug abusing pregnant women, various other parameters --content of amniotic fluid, prostaglandin levels, cortiocosteroid production, estriol excretion, heat stable

alkaline phosphatase levels, liver function studies, serum I_gM levels, and lecithin/sphingomyelin ratios in amniotic fluid--have been studied. Comparing amniotic fluids from normal, diabetic, and drug abusing pregnant women, Singh and Zuspan (1974) did not find any significant differences in prostaglandin content.

Glass et al. (1973) assessed the effects of heroin, which decreases cortisol production in adults by inhibiting ACTH secretion, on fetal and maternal adrenocortical function. Although at the time of delivery addicted mothers had significantly lower serum cortisol levels than did nonaddicted mothers, concentrations were comparable in study and control infants. These discrepancies have not been explained; the authors state that the findings may reflect a decreased responsiveness of the fetal pituitary to heroin or a relative insensitivity of the fetal adrenal cortex to fluctuations in ACTH secretion.

Northrop et al. (1972) studied estriol excretion profiles in narcotic maintained pregnant women during their last trimester. Concentrations of estriol in urine were low, but following narcotic withdrawal, they rapidly increased and sometimes exceeded the average values expected for the gestational time. Neither ACTH nor metopirone stimulated estriol excretion, although a daily dose of 4 mg of dexamethasone decreased urinary estriol excretion. The authors concluded that the drugs a patient is taking must be carefully considered when fetal well-being is monitored with urinary estriol excretion.

Harper et al. (1977) studied levels of placental heat-stable alkaline phosphatase (HSAP) in methadone maintained pregnancies. This enzyme has been reported to be an indicator of placental function; its concentration in maternal serum rises progressively during normal pregnancy and falls after delivery. Because abnormally high values might reflect subtle placental damage, the authors studied levels of this enzyme in methadone maintained addicts throughout pregnancy. High concentrations of HSAP were found in 80 percent of addicted women maintained on greater than 60 mg of methadone per day and in 20 percent of those receiving lower doses. This relationship to dose suggests that methadone may affect the maternal-placental-fetal unit in more subtle ways than previously considered.

Gluck and Kulovich (1973) studied lecithin/sphingomyelin (L/S) ratios in the amniotic fluid in normal and abnormal

pregnancy. Only in normal pregnancy does the L/S ratio correlate with gestational age. The authors found that abnormalities of pregnancy--including maternal, fetal, and placental conditions--may markedly affect the maturation of the fetal lung. Certain conditions associated with maternal hypertension, severe placental problems including retro-placental bleeding, and ruptured membranes accelerate maturation of the L/S ratio, and other conditions (such as diabetes) delay it. Of 10 narcotic addicted patients, all had accelerated L/S ratios. Studies of these individuals suggest that maturation of fetal major organ systems is associated with the L/S ratio, independent of gestational age or birth weight.

Zuspan et al. (1975) studied the effects of detoxification on a pregnant methadone maintained woman. In the middle trimester of pregnancy, a methadone detoxification program was begun. The fetal neurobiological response was monitored by serial amniotic fluid amines (epinephrine and norepinephrine). The detoxification program caused a marked fetal response of the adrenal gland (increase in epinephrine) and sympathetic nervous system (increase in norepinephine), which was blunted when the methadone dose was increased. These investigators thus recommended that detoxification not occur during pregnancy unless the fetus could be biochemically monitored. Unfortunately, many women try to detoxify themselves during pregnancy. Some physicians feel that a drug free status is best and attempt detoxification without appropriate monitoring.

Many investigators (Zelson et al. 1971; Glass 1974; Finnegan et al. 1972; Sussman 1963; Newman 1974) have reported decreased birth weights in infants born to heroin addicted mothers. Although earlier reports did not differentiate between term infants who were small for gestational age and premature infants, it is evident that many of the infants were in fact small for gestational age. It was long suspected that low birth weights were related to poor maternal nutrition and health. Although these factors may be important, laboratory evidence indicates that heroin itself may be a factor in growth retardation (Taeusch et al. 1973; Zagon and McLaughlin 1977; Smith et al. 1974; Hutchings et al. 1976). However, the mechanism by which heroin inhibits growth is not known.

Several investigators have noted that infants born to women who have used methadone have somewhat higher birth

weights than those born to women using heroin (Zelson 1973; Connaughton et al. 1975; Kandall et al. 1976). Kandall's (1976) analysis of birth weights of 337 neonates in relation to history of maternal narcotic usage showed that maternal methadone dosage in the first trimester is directly and significantly associated with birth weight. Thus, in contrast to heroin, which has been found to cause fetal growth retardation that may persist beyond the period of addiction, methadone may promote fetal growth in a dose related fashion after maternal use of heroin.

Not only obstetrical but also medical complications abound in pregnant drug dependent women. Those frequently encountered include: anemia, cardiac disease (often secondary to subacute bacterial endocarditis), cellulitis, poor dental hygiene, diabetes mellitus, edema, hepatitis, hypertension, phlebitis, pneumonia, and tuberculosis. Urinary tract infection--including cystitis, urethritis, and pyelonephritis--is common. Because many women engage in prostitution to support their drug habits, venereal diseases including condyloma acuminatum, gonorrhea, herpes simplex, and syphilis are common. Indeed, medical complications can be seen in nearly 40 to 50 percent of drug dependent women observed in pregnancy (Connaughton et al. 1977).

The drug dependent pregnant woman often develops anemia due to iron and folic-acid deficiency. Nutritional deficiencies in drug addiction result largely from the lack of proper food intake, because the central mechanism controlling appetite and hunger is inhibited. Furthermore, toxic responses to narcotics may contribute to malnutrition by interfering with the absorption or utilization of ingested nutrients. Absorption abnormalities are common in drug addicts because of the high prevalence of lesions of the intestine, liver, and pancreas, and malnutriton is common because of the frequent presence of liver disease. In the chronically addicted individual, when peripheral neuritis sometimes occurs, it is usually due to thiamine depletion, although a deficiency of vitamin B_6, pantothenic acid, or nicotinic acid may produce identical signs. Hypoglycemia, vitamin B_6 deficiency, thiamine depletion, or magnesium deficiency may cause seizures in both alcoholics and drug addicts. Hepatitis, a frequent complication of abuse of injectable drugs, is nutritionally depleting because it causes a loss of protein, vitamins, minerals, and trace elements. Intensive diet therapy is desirable in drug and alcohol

addiction, and parenteral therapy may be necessary to correct fluid, mineral, and vitamin deficits in acutely ill patients (Jones 1974).

Although the obstetrical and medical complications seen in pregnant narcotic dependent women are dramatically increased over that in the general population, one must also be aware of the marked sociological and psychological disruption in this population. Psychological problems occurring in these women include chronic anxiety and depression, low self-esteem, lack of hope for the future, difficulties in interpersonal relationships, and frequent episodes of violence.

Preliminary results of a study comparing the numbers of violent episodes in the lives of pregnant drug dependent women in the Family Center Program in Philadelphia with those in a control population of similar socioeconomic background are startling. Nearly one-third of the former women were beaten as children vs 18 percent for the control group, and nearly three-fourths of the drug dependent women have been beaten as adults. One-quarter of the women were sexually molested or raped as children vs 9 percent of the control group, and one-quarter have been raped as adults vs 4 percent of the control group. Three-quarters of the women have been slapped, punched, or seriously abused by their present partners (Regan et al. 1982). Physical abuse of this kind frequently affects the women psychologically, predisposing them to depression and possible intergenerational patterns of child abuse.

Within the Family Center Program in Philadelphia, women admitted in 1979 and 1980 were assessed using the Beck Depression Inventory in order to determine both the current level of depression and whether depression is a factor contributing to difficulty with parenting. Of the 84 multiparous women tested, 19 percent showed mild, 37 percent moderate, and 19 percent severe depression; thus, 75 percent of the women were depressed. Of the 84 women, 41 percent had children currently in placement with relatives or foster parents. The incidence of moderate or severe depression was significantly higher among the women whose children were in placement than among those whose children were in their own care. Concurrently, depression scores of the Family Center patients were compared with those of a control group of pregnant women from comparable socioeconomic background but assumed to be drug free. The average Beck scores of the Family

Center patients were significantly greater than those in the control group. Our observations, in conjunction with these data, suggest that maternal depression compounds the negative effects of drug abuse on parenting abilities. Depression in pregnant drug abusing women is a significant problem and must be addressed as early as possible in the pregnancy, so that maternal depression may not impair attachment in the neonatal period and interfere with the long-term parent/child relationship (Regan et al. 1981).

EFFECTS OF PRENATAL NARCOTIC ABUSE ON INFANT MORBIDITY

Chromosome Studies

Abrams (1975) studied peripheral blood chromosomes in 34 newborn infants who had been exposed to heroin and methadone *in utero* and 22 newborn controls. He concluded that infants exposed predominantly to heroin *in utero* showed a significantly greater frequency of chromosomal aberrations than did controls, whereas infants exposed predominantly to methadone did not. Adverse environmental factors that may have contributed to the abnormal cytogenetic findings in the heroin exposed infants were less prominent in the methadone exposed infants. The presence of chromosomal rearrangements, including dicentrics and rings, in both groups of drug exposed infants led Abrams to suspect that heroin and methadone can induce chromosome damage *in vivo*.

Amarose and Norusis (1976) assessed chromosomal damage in 99 addicted pregnant women (80 from a methadone maintenance program and 19 heroin addicts) during pregnancy and at delivery, and in their 101 offspring at delivery. About 10 percent of the 27,907 cells scored showed chromosomal aberrations. Chromosome damage was random, affected all chromosomes, and was mainly of the acentric fragment type; the percentage of hypodiploidy was significantly higher than that of hyperdiploidy. In the mothers, dosage and duration of methadone treatment and years of heroin abuse were not correlated with amount of chromosome damage. Likewise, no significant association was found between maternal variables and infant chromosome damage.

Many have been concerned that drug abuse might produce irreversible chromosome damage that could be deleterious. Although chromosomal changes in general are not pathognomonic of narcotic abuse, the increased incidence of chromosomal abnormalities in the lymphocytes from those narcotic abusers strengthens the possibility of a causal relationship. A review of the lifestyles of the 99 subjects did not demonstrate a single instance of aseptic administration of drugs, and there is no way to demonstrate the purity of the preparations. Also, drug addiction was compounded by poor nutrition, lack of rest, stress, increased incidences of tuberculosis, hepatitis, and syphilis, and a lack of early and consistent prenatal care.

Because of the above factors as well as simultaneous polydrug abuse, it is impossible to isolate methadone or heroin as causative agents. Any of the above could have impaired the detoxifying potential of the liver so much that the small lymphocytes became fragile, infected, or primed so that in vitro stimulation into mitosis either elicited existing residual chromosomal damage or engendered chromosome damage. These investigators concluded that the biological implications of chromosome damage cannot be completely understood until it is understood how the human subject reacts when there is no evidence of clinical or pathologic syndromes.

Medical Complications

Medical complications in infants born to drug dependent mothers are generally influenced by 1) adequacy of prenatal care; 2) presence of obstetrical or medical complications (e.g., toxemia of pregnancy, Rh hemolytic disease, hypertension, and infection); and 3) multiple drug use, in which episodes of overdose and withdrawal make the intrauterine milieu unstable and cause hypoxia to the fetus. This hypoxia may predispose the infant to meconium staining and subsequent aspiration pneumonia, which in itself causes marked morbidity and increases mortality.

Most medical complications in neonates born to heroin dependent women result from prematurity. In more than 80 percent of the infants born to heroin addicted women, such conditions as asphyxia neonatorum, intracranial hemorrhage, hyaline membrane disease, intrauterine growth retardation, hypoglycemia, hypocalcemia, septicemia, and hyperbilirubinemia are manifest.

Oleske (1977), in Newark, New Jersey, compared the experiences of 118 infants born to narcotic abusing mothers with those of 2,572 control infants. The former showed higher rates of intrauterine growth retardation, prematurity, postmaturity, meconium staining, jaundice, idiopathic respiratory distress syndrome, positive Australia antigen, positive serology, infection, seizure disorder, asphyxia neonatorum, and gonorrhea ophthalmia. Unfortunately, because this study was a retrospective chart review, the drug histories of many mothers were obscure. Therefore, one can only conclude that the mothers of these infants used variable amounts of nicotine, alcohol, barbiturates, heroin, and methadone for indeterminable periods of time.

In one of the most extensive reviews, Ostrea and Chavez (1979) studied 830 infants born to drug dependent mothers at the Hutzel Hospital in Detroit from 1973 to 1976. Sixty-nine percent of the infants' mothers were clinic patients who used methadone and heroin during pregnancy, whereas 31 percent were infants of non-clinic patients who were on heroin. Compared with 400 infants belonging to a low socioeconomic control group, infants of drug dependent mothers had increased incidences of low birth weight, prematurity, small size for gestational age, and low 1-minute and 5-minute Apgar scores.

Significant postnatal problems, excluding neonatal withdrawal, in the infant born to the drug dependent mothers (Ostrea and Chavez 1979) included: jaundice, aspiration pneumonia (including meconium aspiration), transient tachypnea, hyaline membrane disease, and significant congenital malformations. Congenital malformations were as varied in the infants of drug dependent mothers as they were in controls. Thirty-seven infants of drug dependent mothers had malformations, 20 of which were significant defects, including hydrocephalus, interrupted aortic arch, patient ductus arteriosus, ventricular septal defect, malrotation of the intestines, posterior urethral valves, multicystic kidney, hypospadias, hypoplastic lung, cleft lip, and inguinal hernia. Although these congenital malformations were more common in the infants of drug dependent mothers than in the controls, the incidence of 2.4 percent was not greater than that in the general population. The most significant factors in the morbidity of infants born to drug dependent mothers in this study included intrauterine asphyxia, prematurity, aspiration pneumonia, and hyaline membrane disease.

Palmar crease variance, increase in multiple births, and significant hyperbilirubinemia have also been observed in infants of drug dependent mothers. Dar et al. (1977) analyzed palmar crease variance in a group of high-risk newborns without any evidence of congenital anomalies and found an increased frequency of abnormal creases in each of several groups of "at risk" newborns. There was an apparent association of interrupted transverse creases with intrauterine methadone exposure.

Rementeria et al. (1975) reported that multiple births are more common in drug addicted women than in the general population. In 126 pregnant drug addicts, two sets of twins and two sets of triplets were delivered. The overall multiple birth incidence of one in 32 is three times that in the general population. Three of the four multiple births were dizygotic. The mothers with dizygotic multiple births were receiving moderate to elevated levels of heroin or methadone at the time of conception. The authors postulate that methadone and heroin may directly stimulate the ovary to release an extra follicle or two. Milstein et al. (1974) have reported that drug addicts using heroin for over 2 years have increased mitotic indices and chromosomal replications in their peripheral lymphocytes; heroin may act similarly on the ovaries. However, these narcotics may function indirectly, stimulating the pituitary by way of the hypothalamus to release gonadotrophins (as clomiphene does) which in turn effects the release of multiple ova. Another factor to consider is whether a direct relationship may exist between the narcotic dosage and superovulation.

Several investigators have discussed the effects of narcotic use during pregnancy on neonatal hyperbilirubinemia. It was initially reported that infants born to heroin addicted women are rarely jaundiced (Zelson et al. 1971; Annunziato 1971; Nathenson et al. 1972). The authors postulated that the intrahepatic bilirubin glucuronide transferase activity by opiates, established in mice and suggested in infants of heroin addicted mothers, may not only affect the metabolism of bilirubin but also enhance excretion of other biologic substances requiring glucuronidation, or that other enzyme systems within and beyond the liver may also be induced. However, Zelson (1973) then reported an increased incidence of jaundice in infants born to mothers using methadone. This finding is somewhat corroborated by Ostrea and Chavez (1979), whose population, which also had a higher incidence of

jaundice, consisted of infants born mostly to methadone maintained women.

In Philadelphia, Finnegan et al. (1975) compared infants born to methadone dependent mothers with a control group matched for birth weight and gestational age. Total serum bilirubin levels were determined in the first 4 days of life. Infants predisposed to hyperbilirubinemia (e.g., due to hemolytic disease or sepsis) were excluded. Jaundice occurred in 19 of 24 study infants and 18 of 24 controls. Mean total serum bilirubin levels did not differ significantly between the groups in the first 3 days of life; however, a difference became apparent at 96 hours, with serum bilirubin levels becoming greater in controls than in the study group (9.7 vs 7.1). In addition, average age for peak bilirubin value differed significantly between the groups (study = 59 hours and controls = 71 hours). Thus, this study showed that infants born to methadone-maintained mothers had (1) decreased mean serum bilirubin levels at 96 hours; and (2) lower and earlier peak levels. Different pharmacological actions of heroin and methadone or the use of medications to treat neonatal abstinence may be responsible for differences in the relationships of these two drugs to neonatal jaundice.

Further studies by Connaughton et al. (1977) in Philadelphia under the auspices of Family Center Program, located at Thomas Jefferson University, showed that morbidity in infants born to drug dependent women was directly related to the amount of prenatal care as well as the drug (heroin or methadone) upon which the woman was dependent. Over three-quarters of the infants born to heroin addicts without prenatal care, and a similar fraction of those born to methadone dependent women with insignificant care, suffered neonatal morbidity. Morbidity was lower in infants born to methadone dependent women who had adequate prenatal care. Because of their high incidence of low birth weight and serious morbidity, infants born to heroin dependent women were hospitalized nearly twice as long as those born to methadone maintained women.

In Houston, Wilson (1975) studied the effects of perinatal addiction on somatic growth of infants born to heroin addicted, as well as methadone maintained, women. Intrauterine growth retardation occurred in a large percentage of infants born to mothers addicted to heroin during pregnancy but a somewhat lower percentage of those

whose mothers faithfully attended the methadone program. Birth weights, lengths, and head circumferences were appropriate for gestational age in 28 of 29 infants delivered to mothers participating in the methadone maintenance program for 3 months or longer during pregnancy. During the first year postnatally, linear growth and head circumference were decreased in 35 percent of infants exposed to heroin and 25 percent of infants exposed to methadone during gestation. Complications in the mothers and postnatal infection in the infants were common; both were suspected of contributing to the growth disturbances.

In their study of the outcome of pregnancy in addicts receiving comprehensive care, Green et al. (1979) reviewed many variables in 105 addicted women and their children enrolled in the New York Medical College's Pregnant Addicts and Addicted Mothers Program. They noted that the number of prenatal visits correlated significantly with the neonates' gestational ages and weights at birth. Better neonatal outcomes were associated with joining the program early in pregnancy and frequently attending prenatal care. This group observed the infants to have congenital anomalies (2 percent), meconium staining (9 percent), 1-minute Apgar scores of 6 or less (10 percent), 5-minute Apgar scores of 6 or less (6 percent), and serum bilirubin levels of over 10 mg percent (18 percent).

Similar findings were reported by Finnegan et al. (1976), who compared a group of heroin dependent women and their infants (N=63) with two groups of methadone maintained women and their infants (inadequate prenatal care, N=88, and adequate prenatal care, N=152). Both methadone groups had decreased incidences of obstetrical complications (including preeclampsia), low birth weight, prematurity, and increased average Apgar scores. Of the two methadone dependent groups, the incidences of low birth weight, prematurity, and morbidity were greater in the group receiving inadequate prenatal care. Therefore, these investigators concluded that short-term methadone maintenance with inadequate prenatal care did not significantly improve infant outcome, but that longer methadone maintenance during pregnancy with adequate prenatal care did significantly improve infant outcome.

RISK OF NEONATAL AND INFANT MORTALITY

Obstetrical and medical complications, lack of prenatal care, and low birth weight all contribute to the mortality of infants born to drug dependent women. Most did not survive 20 years ago, when medical scientists lacked the techniques to care for such high-risk infants. During the past decade, with the advent of newer techniques for the care of sick newborns, especially those born prematurely, mortality rates have decreased markedly for infants of drug-dependent women. Thus, the recent figures are 3 to 4.5 percent (Zelson 1973; Finnegan et al. 1977a), in contrast to 94 percent for untreated and 34 percent for treated infants in 1956 (Goodfriend et al.).

Finnegan et al. (1977a) found increased incidences of low birth weight and neonatal mortality among 278 infants of drug dependent women, as compared with 1,586 control infants from the general population delivering at the same hospital. Overall infant mortality in the drug dependent population, composed of both heroin and methadone dependent mothers stratified by adequacy of prenatal care, was 5.4 percent; the figure for the control group was 1.6 percent. Among low birth weight infants, mortality in the drug dependent population was also increased.

Within the methadone dependent group, mortality differed markedly between those with inadequate and adequate prenatal care; it was 10 percent in the former but 3 percent in the latter and 4.8 percent in the heroin dependent group. These results suggest that methadone given in an uncontrolled manner may be more harmful than illicit heroin. There may also be other underlying factors, such as multiple drug abuse. The same trend occurred in the mortality rates for low-birth-weight infants. In general, excess neonatal mortality may be ascribed to the overall lack of health care, with the subsequent occurrence and sequelae of premature birth.

Detailed neuropathological studies, done on 10 to 17 infants who died in the previous study (Rorke et al. 1977), revealed eight categories of lesions, three of which were thought to bear some relationship to the maternal drug dependence. Those three categories that have not been seen in severely ill infants of similar gestational age were gliosis, foci of old infarction, and developmental retardation of the brain. The other lesions identified

included those common to high-risk neonates: germinal plate hemorrhage, acute brain necrosis with and without hemorrhage, germinal plate cysts, and focal subarachnoid hemorrhages. These data imply that most of the adverse effects of addictive drugs may be due to nonspecific secondary gestational complications. Nevertheless, several aspects of the neuropathological findings suggest that the addictive drugs have primary and specific effects on the developing nervous system. The effects of minor degrees of the above lesions on the development of surviving infants have not been investigated. Various investigators (Pierson et al. 1972; Harper et al. 1973; Rajegowda et al. 1976; Finnegan 1979; Chavez et al. 1979) have reported an association between methadone use and sudden infant death syndrome, defined as the "sudden death of an infant or young child, unexpected by a medical history, for which a thorough postmortem examination fails to demonstrate an adequate cause for death" (Valdes-Dapena et al. 1973). It remains uncertain, however, whether the effect is direct or indirect. The findings in the reported cases support various hypotheses relating to the drug's effect on the autonomic nervous system, neonatal abstinence syndrome and its subsequent treatment, chronic fetal hypoxia, and infection. More careful study of previous as well as future cases is needed to clarify how opiate use in pregnancy causes or contributes to the sudden infant death syndrome.

If adequate prenatal services can be provided for pregnant narcotic addicted women, morbidity--including prematurity, asphyxia, infection, and respiratory problems--can be diminished. As morbidity decreases, the mortality rate can approach that among normal infants of the same socioeconomic status.

NEONATAL NARCOTIC ABSTINENCE

Once the umbilical cord of the infant of the narcotic dependent mother has been cut, symptoms of abstinence can be expected. These symptoms have been reported in hundreds of infants by many investigators (Goodfriend et al. 1956; Cobrinik et al. 1959; Hill and Desmond 1963; Kunstadter et al. 1958; Slobody and Cobrinik 1959; Semoff 1967; Mims and Riley 1969), who have recommended many approaches to treatment. Heroin was the major drug of

abuse during the 1950s and 1960s. During the 1970s, reports have described neonatal abstinence syndrome resulting from combinations of heroin and methadone dependence in pregnant addicted women (Finnegan 1978; Zelson 1973; Glass and Evans 1972; Nathenson 1972; Ostrea et al. 1976; Desmond and Wilson 1975; Rothstein and Gould 1974; Finnegan et al. 1974; Finnegan and Reeser 1979; Finnegan 1980).

Onset

At birth, most infants exposed to narcotics *in utero* appear physically and behaviorally normal. Symptoms of withdrawal begin at times ranging from shortly after birth to 2 weeks later, but most appear within 72 hours. The onset of abstinence in individual infants is influenced by many factors, including the type of drug or drugs used by the mother, dosage, timing of the dose before delivery, character of labor, type and amount of anesthesia/analgesia given during labor, maturity, nutrition, and presence of intrinsic disease in the infant. Kandall and Gartner (1972) observed that, in seven infants, significant symptoms first occurred between 2 and 4 weeks of age; irritability and tremulousness were the major late symptoms. Although patterns of drug use varied, methadone was taken in all cases. Fetal accumulation and delayed excretion of the drugs due to tissue binding were thought to account for the delayed onset of symptoms.

Several types of clinical courses may occur (Desmond and Wilson 1975). Withdrawal may be mild and transient, be delayed in onset, increase stepwise in severity, be intermittently present, or have a biphasic course that includes acute withdrawal followed by improvement and the onset of subacute withdrawal. Withdrawal tends to be more severe in infants whose mothers have taken large amounts of drugs for a long period of time. In general, the closer to delivery a mother takes heroin, the later withdrawal begins and the more severe the symptoms in her baby. The maturity of the infant's own metabolic and excretory mechanisms plays an important role. Symptoms can last from 6 days to 8 weeks. Although the infants are discharged from the hospital once drug therapy is discontinued, irritability may persist for 3 months or more, during which the infants may have hyperphagia, increased oral drive, sweating, hyperacusis, irregular

sleep patterns, poor tolerance to holding or to abrupt changes of position and space, and loose stools.

Reddy et al. (1971) report that, for adults, withdrawal symptomatology is of longer duration for methadone than for heroin. The delayed onset of symptoms in neonates is poorly understood. Goodman and Gilman (1970) report that methadone leaves the blood rapidly and accumulates in the lung, liver, kidney, and spleen, and that gradual accumulation and slow excretion of the drug are responsible for the prolonged symptoms. Dole and Kreek (1973) report that, in adults, tissue binding of methadone may explain the prolonged pharmacological action.

Symptomatology

The neonatal abstinence syndrome is a generalized disorder characterized by signs and symptoms of central nervous system hyperirritability, gastrointestinal dysfunction, and respiratory distress, and by vague autonomic symptoms that include yawning, sneezing, mottling, and fever. Initially, the infants appear only to be restless. Tremors begin when the infants are disturbed and progress to the point where they occur when the infants are not disturbed. High-pitched cry, increased muscle tone, and further irritability develop. When examined, the infants have deep tendon reflexes and an exaggerated Moro reflex. The rooting reflex is increased, and the infants are frequently seen sucking their fists or thumbs, yet when fed the infants have extreme difficulty and regurgitate frequently because of uncoordinated and ineffectual sucking and swallowing reflexes. Because of loose stools, decreased intake, and regurgitation, the infants are susceptible to dehydration and electrolyte imbalance.

A group of 138 symptomatic infants born to opiate dependent mothers in Philadelphia were categorized according to withdrawal symptoms. Over 70 percent showed central nervous system hyperirritability evidenced by tremors, high-pitched cries, restlessness, hyperactive reflexes, increased muscle tone, and regurgitation. Increased respiratory rate, poor feeding, hyperactive Moro reflex, and loose stools were seen in over 50 percent. Less common symptoms, mostly associated with the autonomic nervous system, included sweating, mottling, nasal stuffiness, projectile vomiting, watery stools, very high fevers, frequent yawning, dehydration, and convulsions (Finnegan and Fehr 1980).

Respiratory System. Excessive nasal secretions with stuffy nose and rapid respirations, sometimes accompanied by retractions, intermittent cyanosis, and irregular respirations, have been seen in the infant undergoing narcotic withdrawal (Glass et al. 1972; Klain et al. 1972; Lin et al. 1979). Severe respiratory embarrassment occurs most often when the infant regurgitates, aspirates, and develops pneumonia. Increased respiratory rates associated with hypocapnia and increased blood pH occur during the first week of life in infants undergoing abstinence. This respiratory alkalosis is thought to assist in binding indirect serum bilirubin to albumin and possibly in preventing the respiratory distress syndrome, which is rarely observed in infants of heroin addicted mothers. On the other hand, alkalosis can decrease the levels of ionized calcium and lead to tetany (Glass et al. 1971). Klain et al. (1972) have reported that some of the symptoms in infants of addicted mothers may be directly related to alkalosis.

Although the frequency of respiratory distress syndrome increases with decreasing gestational age in premature infants whose mothers are not addicted to heroin, Glass and associates (1971) noted no respiratory distress syndrome among 33 premature infants born to heroin addicted mothers at the Harlem Hospital Center. This study compared addicted infants with nonaddicted premature infants having gestational ages of 32 to 37 weeks.

Because newborns have decreased levels of 2,3-diphosophoglycerate (DPG), they cannot unload oxygen effectively at the tissue level. At Philadelphia General Hospital, studies of the status of this enzyme were performed in infants of drug dependent mothers in an effort to determine if a maturing effect was associated with prenatal exposure to drugs of abuse. Cord blood and maternal venous blood were obtained, and the P_{50} (partial pressure of oxygen at which hemoglobin is 50 percent saturated), hematocrit, and red cell 2,3-DPG levels were measured (Finnegan et al. 1974). None of the infants monitored for signs and symptoms of hyaline membrane disease showed evidence of the disease. Mean values of P_{50} in the cord blood and total 2,3-DPG in muM/ml of RBCs were higher in the opiate addicted infants than in normal controls. (Maternal values of both were slightly elevated, as compared with those in normal controls.) Under normal conditions, term infants achieve such a shift of the oxygen hemoglobin equilibrium curve to the right by the sixth to the ninth week of life. Thus, newborn infants

of opiate dependent mothers seem to achieve tissue oxygen unloading comparable to those of 6-week-old term infants; opiates may function as enzyme inducers, increasing blood levels of 2,3-DPG and decreasing oxygen affinity.

In sequential pulmonary function studies by Lin et al. (1979), infants of drug dependent mothers appeared to show transiently lower lung compliance and tidal volume from birth to 24 hours of age than did normal control infants. By 3 days of age, lung compliance and tidal volume reached normal levels in spite of persistent tachypnea and abstinence symptoms.

While evaluating the sweating deficit of premature infants, Behrendt and Green (1972) noted that 30 of 131 healthy full-size babies and two of 108 healthy low-birth-weight babies showed spontaneous generalized sweating under standardized conditions. In contrast, eight of 20 low-birth-weight infants of heroin addicted mothers had spontaneous generalized sweating. In addition, the pharmacological threshold for sweating was lower in low-birth-weight infants of addicted mothers than in healthy low-birth-weight controls. The authors suggest that this paradox may result from the predominantly central-neurogenic stimulation of sweat glands by heroin withdrawal.

Sleep Disturbances. Infants undergoing narcotic withdrawal have seriously disturbed sleep. Sisson et al. (1974) studied electroencephalographic tracings and electromyographic recordings of eye and mouth movements simultaneously before, during, and after treatment of heroin and methadone withdrawal in 10 infants. They concluded that a) narcotics obliterate rapid eye movement (REM) sleep in the neonate; b) withdrawal prevents normal adequate periods of deep sleep; c) proper therapy causes REM sleep and deep sleep cycles to return; and d) therapy can be regulated by interpreting polygraphic recordings rather than relying on observations of more gross signs and symptoms of withdrawal.

Dinges et al. (1980) studied neonatal sleep as a measure of central nervous system disturbance in infants exposed prenatally to narcotics. The 28 infants chronically exposed *in utero* to low doses of methadone, with or without concomitant heroin, displayed more REM sleep and less quiet sleep than did 30 control infants. Babies prenatally exposed to both opiates and nonopiates have less organization of sleep states.

Seizure Activity. One of the most serious symptoms of neonatal abstinence is the development of seizures. Reported effects of methadone versus heroin on the occurrence of seizures during neonatal abstinence have varied (Zelson et al. 1971; Goddard and Wilson 1977; Herzlinger et al. 1977; Finnegan 1979; Zelson et al. 1971), and Herzlinger et al. (1977) noted a greater incidence of seizure activity among 362 infants of methadone dependent mothers. Generalized motor seizures or rhythmic myoclonic jerks were most commonly seen. Abnormal electroencephalographic activity was found only during the active seizure phenomenon; interictal tracings were normal. Seizure occurrence and myoclonic activity were not related to maternal dosage of methadone, although no blood levels of methadone were obtained in Herzlinger's study. In contrast, among more than 150 infants examined, Goddard and Wilson (1977) saw only one seizure attributable to abstinence in infants born to heroin or methadone addicted mothers. In the Family Center Program Study in Philadelphia (Finnegan 1979), of almost 400 infants born to methadone maintained women, as well as those born to women dependent on opiates and nonnarcotic psychotropic agents, only five cases of confirmed seizure activity have occurred. In infants undergoing neonatal abstinence syndrome, the relationships of seizure activity, prenatal maternal drug usage, and abnormal electroencephalographic findings to long-term prognosis are unclear.

Factors Affecting Severity of Neonatal Abstinence. By the middle 1970s, nearly 80 percent of pregnant addicted women in New York City were using methadone alone or in combination with heroin. Similar experiences occurred in Philadelphia, where 80 percent of drug dependent women who delivered were on methadone and combinations of methadone and heroin. Various investigators have disagreed markedly with regard to the differences in withdrawal symptoms associated with heroin versus methadone in newborn infants. Blatman (1971) proposed that methadone babies were "better off" because of the superior pre- and postnatal care available to women treated in methadone maintenance programs. Blinick (1971) reported mild to moderate withdrawal symptoms in approximately half of 19 infants addicted to methadone; none developed severe symptoms. Zelson (1971), in his study of 34 infants born to mothers who had used methadone alone or in combination with heroin and 24 born to mothers who used heroin only, reported that the severity of withdrawal, number of signs, and frequency of seizures were higher in methadone babies.

Rajegowda et al. (1972) found that withdrawal symptoms were more common and lasted longer among methadone addicted infants than among heroin addicted infants. Mothers in Rajegowda's study received 80 to 160 mg methadone/day, but those in the Blinick study (1971) received 60 to 120 mg/day. Neither Rajegowda nor Zelson indicated whether dosages were comparable in the heroin and methadone exposed babies; although methadone dosages could be accurately identified from the programs providing methadone to the mothers, the amounts of heroin were strictly speculative. In Chicago, Davis et al. (1975) found that 80 percent of infants born to addicts maintained on low doses of methadone (mean of 45 mg/day) had evidence of withdrawal, but fewer than one-third showed signs severe enough to require therapy.

Subsequent studies addressed the pharmacology of methadone in relation to abstinence symptoms. Blinick et al. (1975) determined concentrations of methadone in maternal plasma and urine, as well as amniotic fluid, cord blood, fetal urine, and breast milk. No simple relationship between methadone levels in the neonate and the intensity of the withdrawal syndrome was seen. They concluded that multiple drug abuse and other undetermined factors may influence the severity of withdrawal signs in the neonate.

In Detroit, Ostrea et al. (1976) prospectively studied 196 drug addicted mothers and their infants to determine the maternal, fetal, and environmental factors that may affect the severity of narcotic withdrawal in newborns. Severity of withdrawal was not related to infant gestational age, sex, race, Apgar score, maternal age, parity, duration of heroin intake, or level of morphine measured in the infant's urine or blood. Reducing the amount of illumination and noise in a study nursery did not lower the incidence of severe neonatal withdrawal. However, the severity of withdrawal in the infant was significantly correlated with maternal methadone dose. The Detroit group recommended that the mother be given a low dose of methadone (less than 20 mg/day) as soon as safely possible to prevent serious withdrawal in her infant.

Similar conclusions were reached by Madden et al. (1977), who found that frequency of withdrawal symptoms and need for treatment were significantly reduced in infants born to mothers whose methadone dose at the time of delivery was less than 20 mg/day.

In New York City, Rosen and Pippenger (1976) studied the relationships among maternal dose of methadone, incidence and severity of neonatal signs of withdrawal, and placental transfer of drug, as well as that between maternal and neonatal plasma levels of methadone. They found that the relationship between maternal dose of methadone and incidence of neonatal withdrawal symptoms was unpredictable. However, the time and incidence of withdrawal symptoms were closely related to the last maternal dose of methadone. In addition, neonatal withdrawal symptoms were related to individual variations in maternal metabolism and to placental transfer of methadone, as well as to individual variations in the rate of excretion of methadone as reflected in neonatal plasma halflife. At plasma levels of methadone greater than or equal to 0.06 mcg/ml, withdrawal did not appear to occur; but when plasma concentrations fell below this level, symptoms began within 24 hours.

Also in New York City, Harper et al. (1977) studied the relationship between maternal methadone dosage and severity of subsequent neonatal methadone withdrawal. Severity of abstinence symptoms was found to be positively correlated with the total amount of methadone ingested by the mother during the last 12 weeks of pregnancy, the maternal dose of methadone at the time of delivery, and the intrapartum maternal serum methadone level.

Kandall et al. (1977) reported on 230 infants born to drug dependent women and 33 infants born to exaddicts in New York City during 1971-74. Neonatal withdrawal from methadone appeared to be more severe than that from heroin, since the amount of medication required to control symptoms and the duration of treatment were greater. Central nervous system signs were the most common manifestations of withdrawal in all the groups studied. Severity of withdrawal did not correlate with late-pregnancy maternal methadone dosage.

In yet another New York study (Green et al. 1979), which included 105 addicted women enrolled in the New York Medical College's Pregnant Addicts and Addicted Mothers Program, maternal methadone dose at the time of delivery correlated significantly with the neonatal withdrawal status. Although abstinence occurred in 73 percent of the infants, less than a third of the cases needed treatment. Most of the infants were managed by swaddling and by feeding more often. Duration of treatment ranged from

5 to 13 days for all but one infant, for whom it was 39 days.

In a study comparing methadone maintained women and street heroin addicts, Connaughton et al. (1975) found improved outcome in infants of the former. Among 260 infants of drug dependent mothers, the incidence of severe withdrawal was 12.5 percent for infants of mothers on methadone but 25 percent for those of mothers on heroin only.

In Philadelphia, Finnegan and Reeser (1977) studied the effect of average maternal daily dose of methadone during pregnancy on two groups of infants. The first group (106 mothers) had inadequate, while the other group (186 mothers) had adequate, prenatal care. The average daily doses of methadone were similar for both groups (27 and 30 mg, respectively). Those infants born to the mothers with adequate prenatal care had better outcomes with regard to general neonatal variables. For all infants, severity of withdrawal syndrome increased with the average maternal daily dose of methadone; mild or moderate abstinence was associated with average daily doses of 35 mg and below. No statistically significant differences in severity of withdrawal syndrome were found when the infants were stratified at term appropriate for gestational age, premature, or intrauterine growth retarded. Because the average daily doses of methadone were very similar for the two groups, it appears that the doses alone did not contribute to the different infant outcomes but that the amount of prenatal care played a significant role.

The results of the previous studies may reflect the relative potencies, lengths of action, and available doses of heroin and methadone. Methadone programs supply the mother (and the infant) continuously with a long-acting pure narcotic, while street addicts encounter unpredictable changes in availability and purity of a shorter-acting agent (heroin).

In evaluating infants of drug dependent women, the clinician must be aware that symptoms of neonatal narcotic abstinence may mimic those of many very serious--and indeed, potentially lethal--neonatal conditions, such as hypoglycemia, hypocalcemia, other metabolic disturbances, meningitis, and intracranial hemorrhage. Other drugs used by the mother must be identified in order to decide whether the infant is withdrawing from narcotics or from

barbiturates, tranquilizers, or other sedative-hypnotics. Loose stools may result from abstinence, but one should also consider the possibility of infection. The same logic applies when fever occurs. Although neonatal hyperthyroidism is rare and usually is associated with a clear-cut history of maternal disease, it is one of the few conditions that can mimic the withdrawal syndrome's marked irritability, hyperactivity, tremors, sweating, sleeplessness, and loose stools.

Fortunately, appropriate treatment of neonatal abstinence prevents mortality and permits a return to a normal physiological state. Careful assessment utilizing a neonatal abstinence scoring system and appropriate treatment and detoxification are essential in bringing the infant into a state of general good health (Finnegan 1978).

BEHAVIORAL AND DEVELOPMENTAL EVALUATION OF INFANTS EXPOSED TO NARCOTICS IN UTERO

The Neonatal Period

Many investigators have delineated the neonatal, as well as the long-term, behavioral and developmental effects of narcotics in animals (Sonderegger 1976; McGinty and Ford 1976; Glick et al. 1977; Zimmerberg et al. 1974). Several others have studied the effects of prenatally administered narcotics on human infants (Soule et al. 1974; Strauss et al. 1975; Lodge et al. 1975; Kron et al. 1976; Kaplan et al. 1975, 1976). The latter studies have used the Brazelton Neonatal Behavioral Assessment Scale, objective measures of the sucking reflex, and electrophysiological recordings.

Brazelton Neonatal Behavioral Assessment Scale (BNBAS). The BNBAS has been extensively used to evaluate newborn behavior in various populations including normal newborns, infants exposed to pharmacologic agents during labor, and infants exposed prenatally to drugs of abuse. This scale evaluates habituation to stimuli such as a light and a bell, responsivity to animate and inanimate stimuli (face, voice, bell, rattle), state (sleep to alertness to crying), and lability of state change (i.e., as irritability and consolability), and neurologic and motor development.

Soule et al. (1974) used this scale to study control infants and those born to heroin addicted mothers on methadone maintenance. Nineteen infants who were exposed prenatally to methadone and had received no pharmacologic treatment before the first exam were compared with 41 infants in an unrelated developmental study. Testing occurred at 48 and 72 hours of age. Group differences on the Brazelton Scale scores clearly indicate that the infants exposed to methadone were undergoing narcotic withdrawal. Typically, these infants were restive and tended to be neurologically irritable. They cried more often and were state labile. In addition, they were more tremulous, hypertonic, and manifested less motor maturity than the nonexposed infants. Responsiveness to visual and auditory stimuli also differed. While responsive to auditory stimuli, the methadone subjects responded poorly to visual stimuli. They seemed uncomfortable when opening their eyes and attempting to focus (pupil size was within normal limits). Although differences in scores suggested drug withdrawal, other characteristics such as parity, socioeconomic conditions, race, birth weight, and prenatal care must be considered.

Strauss et al. (1975) also used the BNBAS to study the behavior of narcotic addicted and nonaddicted newborns in the first 2 days of life. The classic signs of narcotic abstinence were observed. Specifically, the addicted infants were less able to be maintained in an alert state and less oriented to auditory and visual stimuli, with deficits most pronounced at 48 hours of age. Although the addicted infants were substantially more irritable, they, like the normal neonates, were capable of self-quieting in response to soothing intervention. Strauss suggested that these characteristics may affect caregivers' perceptions of infants. Depending on their extent and duration, these manifestations may have long-term consequences for the development of the infant/caregiver interaction patterns.

Using the BNBAS, Kaplan (1975) studied 22 infants born to mothers receiving methadone and 11 in a control group with no history of maternal narcotic addiction. Sucking performance was concurrently measured in 16 of the methadone exposed babies. It was found that 10 of the behavioral items on the BNBAS significantly discriminated between neonates born to narcotic addicted mothers and the controls; the correlations between the scores on these 10 Brazelton items and rate of sucking were significant. An unexpected finding was that both the sucking measures and

the Brazelton items were highly correlated with birth weight, that is, lower weight babies tended to be more behaviorally affected by maternal addiction.

When the BNBAS is used to evaluate infants born to methadone maintained women, the most consistent differences are for those items corresponding to clinical features of the abstinence syndrome, i.e., irritability, tremulousness, jerkiness of motor movement, and increased muscle tone. Kaltenbach et al. (1981) studied 35 infants born to methadone maintained women. The BNBAS was used but was scored using the a priori cluster method in order to indicate the infant's availability for interaction responses to inanimate visual, inanimate auditory, animate visual, and animate auditory stimuli, as well as the infant's alertness, cuddliness, and consolability. Scores for the Interactive Dimension were: 1 = superior; 2 = adequate; 3 = deficient. At 1 day of age, all infants later requiring treatment had average scores deemed "adequate." By 30 days of age, 13 of the 35 infants had superior scores and 17 had adequate scores. The five infants with deficient scores were those who had severe withdrawal symptoms that remained difficult to control. For the infants still being treated at 30 days, those whose mothers rarely visited had far lower mean scores than those whose mothers visited regularly (2.6 vs 1.8). Poor interaction of the infants may have caused avoidance by the mothers, or maternal attention may have improved the infants' interaction. These data suggest that neonatal abstinence syndrome has a deleterious and complex effect on infant/caregiver interaction.

In another study by Kaplan et al. (1976), passively addicted infants, high-risk infants, and normal infants were evaluated using the BNBAS at 3 and 28 days of age. Over this period, alertness and irritability scores remained highly stable in normal infants but increased in the other groups. At 3 days of age, the normal control group was more alert than both the high-risk and passively addicted groups. By 28 days of age, however, there were no significant differences among the alertness scores of the three groups. The irritability scores were consistent with those expected in infants undergoing abstinence. At 3 days of age, passively addicted infants appeared more irritable than both control populations, although the differences were not statistically significant. At 28 days of age, however, the passively addicted infants were more irritable than the high-risk and normal. During the period, irritability scores did not

change for the normal infants but tended to increase for the other groups. These findings suggest that the passively addicted infants may have continued to experience subclinical withdrawal that could have benefited from additional therapy with pharmacologic agents.

Behavioral and Electrophysiological Characteristics. The behavioral electrophysiological characteristics of infants born to narcotic addicted mothers were studied by Lodge et al. (1975). The neonatal characteristics of 29 infants born to heroin addicted mothers receiving varying dosages of methadone during pregnancy were compared with the characteristics of 10 normal infants in a control group. The neonatal withdrawal period was characterized by heightened auditory responsiveness and orientation, lowered overall alertness, and poor reaction to visual stimuli. Electroencephalographic recordings showed high-frequency dyssynchronous activity suggestive of central nervous system irritability. Analysis of evoked-response data further corroborated the behavioral findings with evidence for low arousal value of visual stimulation in the vertex frequency characteristics and poorly defined occipital responses. Auditory evoked responses appeared better integrated. The long-range developmental significance of these findings needs further evaluation.

Effects of Drug Treatment During Abstinence. Neonatal nurses caring for infants experiencing abstinence have clinically documented the uncoordinated and ineffectual sucking and swallowing reflexes. Kron (1967, 1968) developed a precise instrument for studying the rate, pressure, and organization of sucking as well as the amount of nutrients consumed. Measures of nutritive sucking were used to monitor the severity of abstinence in infants born to narcotic dependent mothers maintained on methadone and to street heroin addicts. Control populations consisted of normal full-term infants whose mothers had received no obstetrical analgesia or anesthesia and those born to toxemic mothers who had received magnesium sulfate. Mothers maintained on methadone during pregnancy received a mean daily dose of 42 mg.

Within 24 hours after delivery, all 50 infants showed some degree of abstinence symptoms. Twenty-eight of the infants were treated with phenobarbital; five with paregoric; six with diazepam; and three with chlorpromazine. Abstinence symptoms in the remaining eight infants were not considered severe enough to require drug treatment. The sucking rates, per minute, averaged over six trial

feedings during the first 3 days of life, were nearly 40 in the normal controls, 32 in the infants born to toxemic mothers, 18 in the infants exposed to methadone, and 26 in those exposed to heroin. On the first day, during the first two trials, the babies of toxemic mothers had scores similar to those of infants exposed to heroin and methadone. They rapidly recovered, however, and their scores approached those of normals. The scores of infants exposed to heroin and methadone remained depressed throughout. Because the trials were done only over the first 3 days of life, one cannot be sure how rapidly the methadone dependent infants could have recovered. It is postulated that because of the longer action of methadone, the effects may have been more prolonged than those of heroin.

In additional studies, Kron et al. (1974) evaluated the effect of detoxicant treatment for abstinence on sucking behavior. Infants treated with paregoric tended to suck more vigorously than those treated with sedatives such as phenobarbital and those receiving no therapy at all; they approached normal control levels on most of the parameters. The infants who received no treatment had consistently lower averages than the paregoric treated babies, although their withdrawal symptoms were judged too mild to warrant drug therapy. Feeding behavior of infants treated with diazepam was greatly depressed.

Kron et al. (1974) also studied the effects of maternal dosage and length of time on methadone on the sucking behavior of newborns. The findings suggest that the length of time that a mother is enrolled in a methadone maintenance program, and to a lesser degree the dosage level at the time of delivery, account for a significant portion of the variance in newborn sucking behavior.

Studies Beyond the Neonatal Period

Although the newborn exposed to pharmacologic agents *in utero* may be normal physically, behaviorally, and neurologically, one cannot assume that no effect has occurred; the effects of pharmacologic agents may not become apparent for many months or years. Therefore, long-term follow-up of infants prenatally exposed to pharmacologic agents is extremely important. Evaluations of infants born to women who have taken illicit drugs are somewhat more difficult than are those of infants involving the use of licit drugs. Despite this difficulty, several

studies on human infants exposed to narcotic agents prenatally have been reported (Ramer and Lodge 1975; Sardemann et al. 1976; Strauss et al. 1976; Finnegan et al. 1977b; Green and Zarin-Ackerman 1977; Kaltenbach et al. 1979; Wilson et al. 1979).

The limitations of these studies include inadequate numbers of subjects, inability to eliminate confounding variables such as differences in social milieu, exact identification of drugs used during pregnancy, neonatal conditions, parenting skills, and the effect of the primary caretaker. Most studies encompass only the first or second year of life, and only a few look at children beyond the fourth year. Also, they have reported summary scores instead of isolating particular variables associated with a child's development. Many of the studies are cross-sectional rather than longitudinal. Very little is known about these children's behavior and learning skills in school. Therefore, investigators have just begun to look into the vital area of the long-term effects of prenatal narcotic agents. This section summarizes those findings currently available.

Wilson et al. (1973) observed the growth and development of 30 infants born to heroin addicts from 3 to 34 months. Eighty percent had signs of neonatal withdrawal, and 60 percent also showed subacute withdrawal signs for 3 to 6 months. Seven of 14 infants observed for 1 year or longer had behavioral disturbances (predominantly hyperactivity), brief attention span, and temper outbursts, while two had neurological abnormalities. Growth impairment was associated with behavioral disturbances, which appeared to be unrelated to subsequent environmental factors, in four of the seven infants. Infants performed at age-appropriate levels on behavioral testing using the Gesell Schedule. The fact that most of the infants were being raised either in foster homes or by family or friends may have influenced the results. Furthermore, the sample size of 14 is too small for drawing any generalizable conclusions.

In a city-operated methadone maintenance program in San Francisco, Ramer and Lodge (1975) studied 35 infants born to 32 registered mothers. Bayley Scales of Infant Mental and Motor Development were used to evaluate the infants at 3-month intervals during the first year and at 6-month intervals during the second and third years. Sixty percent of the infants showed mild or no symptoms of neonatal abstinence and the rest developed moderate to severe symptoms of withdrawal. Symptoms were most severe

in infants of mothers with documented histories of poly-drug abuse. In the neonatal period, many of the infants were slow in gaining weight; afterward, however, growth and development generally were in the normal range. Older infants showed age-appropriate development in vocalization and language, but their performance on perceptual motor tasks was somewhat less adequate. This study did not evaluate the relative impacts of genetic, prenatal, and subsequent environmental factors on overall development. Furthermore, the developmental quotients during these early years, although useful in identifying areas of strength and weakness, are not predictive of subsequent intelligence quotients. Nevertheless, these results suggest that providing a modified methadone maintenance program--including good prenatal care and nutrition, neonatal care, and continued support and encouragement of the mother after the birth of the child--may offset the detrimental effects of the neonatal withdrawal experience on the infant and foster an environment that may facilitate normal development.

Nineteen children born to narcotic addicted women were evaluated by Sardemann et al. (1976). Of the 16 infants who had withdrawal symptoms, 11 required medical treatment for them. One infant died of congenital malformations. Of the surviving 18 infants, 14 were discharged to their mothers, and four went to a children's home. During follow-up, which varied from 2 months to 2.75 years, 10 of the children had to be placed in a children's home for a period of time. No physical abnormalities were found in any of the children. Motor and perceptual development were normal in 12 children, but speech development was delayed in three. Because of the nature and size of this study, conclusions cannot be extrapolated.

In Detroit, at the Hutzel Hospital's Methadone Treatment-Perinatal Care Program, Strauss et al. (1976) compared evaluations of 60 infants born to narcotic addicted women with those of 53 controls. The infants' psychological development was evaluated with the Bayley Scales of Infant Development at 3, 6, and 12 months of age. In addition, anthropometric measurements were obtained at 12 months of age for 21 study and 24 control infants. These investigators concluded that the average course of infants born to addicted mothers is well within the normal range throughout the first year of life. However, their

data show that these children's level of psychomotor development declines throughout the first year. The difficulty with motor development at 12 months of age was primarily in the area of locomotion; in particular, the study infants were significantly less likely than the controls to be walking unaided at this age. The authors stated that the decline did not appear to be an artifact, for a similar decline was noted between 3 months and 1 year of age in another cohort. Whether this finding reflects some endogenous process or influences in the caregiving environment remains uncertain. Repeated evaluation of these individuals' behavioral development during infancy and childhood, as well as assessments of their environment, are necessary to specify more clearly the degree and determinants of risk for developmental dysfunction in this population.

In the specially designed comprehensive program for pregnant drug dependent women (Family Center) in Philadelphia, follow-up studies on infants born to methadone maintained women are in progress. In this program, as in many in the United States, there has been much concern about the effects of methadone maintenance during pregnancy on the fetus and neonate. The initial outcome for the neonate seems favorable with regard to physical conditions, although concern exists about the severity of neonatal abstinence. Until recently, the long-term effects of prenatal methadone were unknown. Recent literature has indicated that, in general, infants born to methadone dependent women show mental and motor development in the normal range through the first year of life.

In Family Center, 59 infants born to women maintained on methadone during pregnancy were evaluated periodically for development and physical growth and compared with a control group of 42 infants randomly selected from the same socioeconomic class delivering at our hospital. No drug use was evident in the control group. The infants were evaluated by the Gesell Developmental Schedule. We found that from birth through 89 weeks of age, children of mothers maintained on methadone during pregnancy were lighter and shorter than the controls. Statistical analysis of measurements from birth through 38 weeks showed that although the study group was consistently below the 50th percentile for weight and height, it did not demonstrate growth lag in comparison to the control group. Furthermore, the study group did not have any unusual or significant health problems as compared with the control group, and there were no abnormal neurological findings.

There was no correlation between maternal drug intake, degree of neonatal withdrawal, and Gesell Behavioral Profiles of the infants through 24 months of age (Finnegan et al. 1977b).

In another study from Philadelphia's Family Center, the developmental status of infants exposed to methadone in utero and non-drug-exposed infants were assessed at 1 and 2 years of age. Fifty-three 12-month-old infants (26 drug exposed and 27 controls) and 41 24-month-old infants (17 drug exposed and 24 controls) were assessed with the Bayley Scale of Mental Development and a neurological examination. Findings on the latter were normal in all infants. At 12 months of age, the mental developmental index (MDI) was within the normal range for both groups, although the scores for the drug exposed group were somewhat lower. At 24 months, the MDI did not differ between the groups. Differences occurred, however, in failure rates on specific items. Also, in both Family Center and control infants, scores were lower at 2 years than at 1 year. The decrements for both groups were significant and suggest that environment may confound long-term outcome (Kaltenbach et al. 1979).

In Philadelphia, we have begun a longitudinal study of infants born to methadone maintained mothers in an effort to evaluate outcome from birth through 5 years of age. Preliminary data on 50 infants evaluated by the Bayley Scales of Infant Development at 6 months of age show significant differences between male and female infants born to methadone maintained women but no significant differences between infants born to drug dependent women and the population norm. One-half of these infants have had their 12-month evaluations. Results reveal that there is a significant decrease in Bayley Scores for male infants from 6 to 12 months of age, resulting in no difference in scores between males and female infants by 12 months of age. None of the evidence indicates that infants of drug dependent women are below the population norm at 12 months of age.

One may interpret these data according to several known hypotheses as well as some speculations. Sex differences are documented in the literature showing that males are superior in gross motor skills and females are superior in verbal skills. Males are more physically vulnerable, with higher morbidity and mortality. We speculate that factors contributing to differences noted above include the following:

(a) Limited evidence suggests that black mothers of low socioeconomic class pay more attention to male than female offspring. Males are stimulated more and therefore, because of their inherently superior gross motor skills, score higher on the Bayley Scales by 6 months of age.

(b) Male partners are more often present during early than late infancy and may stimulate male more than female infants.

(c) During infancy, male infants may receive more physical stimulation, whereas females may receive more verbal stimulation.

(d) The 6-month Bayley Scores are affected more by motor than verbal skills.

Probably the sex differences observed at 6 months of age disappear by 12 months because as the child becomes older and more demanding, the male is no longer favored and indeed may be replaced in the attentions of the mother by a new infant or a pregnancy. By 12 months of age, fine motor skills, at which females excel, are developing. Also, the male child may no longer be receiving as much stimulation from the adult male in the household. Most importantly, the data indicate that infants born to methadone maintained mothers are performing within the normal range on the Bayley Scales of Infant Development at both 6 and 12 months of age (Kaltenbach 1982).

In another longitudinal study, in New York City, Rosen (1981) evaluated the developmental effects of prenatal methadone exposure by comparing 41 infants born to methadone maintained mothers with 23 children from matched backgrounds but without maternal history of drug abuse. At 6 months of age, each child received physical and neurological examinations and behavioral assessments including a visual habituation task, the Bayley Scale of Infant Development, and the Object Performance Scale. The experimental subjects and the controls did not differ significantly in frequency of suspected neurological signs or in mean scores on the three behavioral measures. Despite the great difference within group variances, performance on the behavioral measures was not related to maternal or neonatal characteristics.

In a continuation of this longitudinal study (Rosen et al. 1981), the 40 study subjects and 25 controls received developmental and neurological evaluations at 2, 4, 6, 8,

10, 12, 15, and 18 months of age. The children of methadone maintained mothers showed (1) a significantly higher incidence of otitis media; (2) a significant number of head circumferences below the third percentile; (3) neurological problems including muscle tone discrepancies, developmental delays, poor fine motor coordination, and a high incidence of visual abnormalities; and (4) significantly lower scores on the Bayley Mental and Motor Developmental Indexes. Although scores on the Bayley Scales differed significantly from those of the comparison group, they were within the accepted norms for the overall population. The authors caution that the neurobehavioral findings in the children of methadone maintained mothers at 18 months of age may be predictors of later learning and behavioral problems and thus warrant follow-up.

In a cross-sectional study, Kaltenbach et al. (1978) evaluated the development of 50 experimental and control children at 4 years of age. Thirty-three of these children were born to women who received methadone during pregnancy, as well as prenatal care, while enrolled in the Family Center in Philadelphia. The 17 control children were randomly selected from a stratified population of comparable socioeconomic, racial, and medical backgrounds from a pediatric outpatient clinic. The children were assessed using a routine neurological examination, the Wechsler Pre-school and Primary Scale of Intelligence, the Test of Language Development, Initiation of Gestures, and the Motor-Free Visual Perception Test. On the Wechsler scale, differences between experimental and control children were very small and not statistically significant. Both groups performed better on the verbal scales than on the performance scale. Furthermore, there were no differences in results of the tests of perception and language. All neurological findings were within the normal range, and severity of neonatal withdrawal was not related to I.Q. score (Kaltenbach et al. 1979). These data suggest that 4-year-old children who were born to women maintained on methadone and who experienced neonatal abstinence had mental development in the normal range. Likewise, language and perceptual skills of these children and those of comparable backgrounds whose mothers were not involved with drugs did not appear to differ.

Wilson et al. (1979) studied 3-to-6-year-old children of heroin addicted mothers and compared them with three other groups, matched for age, race, sex, birth weight, and socioeconomic status. The study included 22 heroin

exposed, 20 drug environment, 15 high-risk, and 20 control infants. Heroin exposed children weighed less and were shorter than those in the comparison groups, with 14 percent having head circumferences below the third percentile. These children also differed significantly from the others in perceptual measures and on subtests of the Illinois Test of Psycholinguistic Abilities and the McCarthy Scales of Children's Abilities relating to the process of organization. This study suggests that chronic intrauterine exposure to heroin may affect growth and behavior, as well as perceptual and learning processes, in preschool children. Although heroin was the primary drug of abuse in this study, many of the mothers had histories of multiple-drug abuse. The functional deficits were sufficient to impair cognitive development, but because of differences in behavior and perceptual and organizational abilities, these children must be considered vulnerable to suboptimal social and environmental conditions.

In summary, findings noted above suggest that infants born to heroin addicted mothers, especially those using heroin along with other psychoactive agents, have a less favorable outcome than do those born to methadone maintained mothers given prenatal care. Unfortunately, because of inadequate sample sizes and methodological limitations, most of the studies reported cannot be considered conclusive. Future studies should evaluate particular variables within a child's development instead of depending upon summary measures. Also, more longitudinal studies are necessary to permit appropriate conclusions to be drawn. Most importantly, children of school age must be evaluated with regard to both behavior and learning ability.

CONCLUSIONS

As the epidemic of drug abuse has increased over the past decade, bringing with it numerous complex problems, a significant health dilemma for which solutions must be found has occurred in the United States and many countries of the world. Despite the accepted belief that opiate dependency suppresses hypothalamic function and thus impairs fertility (Cushman and Kreek 1974), the number of births to addicted women has risen steadily during the 1960s and 1970s, in part because the number of addicted women has increased rapidly. Many investigators

have reported high rates of obstetrical and medical complications among pregnant addicts and morbidity and mortality among passively addicted newborn infants that far exceed those in other high-risk maternal and infant populations. Unfortunately, there are insufficient data on the long-term effects of maternal drug usage. In addition, controversy exists on how best to prevent and treat the adverse sequelae of addiction. However, initial data have shown that programs providing comprehensive care for addicts significantly reduce morbidity and mortality for both mothers and infants. Further studies are needed to investigate whether the mothers can be assisted through education, counseling, and early diagnosis and treatment of mental disorders.

The successes of various approaches reported in the literature--as well as the paucity of specific conclusions with regard to prevention, treatment, and long-term outcome--lead to the following recommendations for treatment and further research.

Treatment

1. The pregnant woman who abuses drugs must be designated "high risk" and warrants specialized care in a perinatal center giving her comprehensive addictive and obstetrical care and psychosocial counseling.

2. Addictive care of the pregnant woman may involve voluntary drug-free therapeutic communities, methadone detoxification (depending on the time in pregnancy that it is requested), or methadone maintenance. When appropriate, low-dose methadone maintenance with substantial medical and paramedical support should be instituted. Detoxification, if requested or necessary, should preferably occur between the 16th and 32nd weeks of gestation and should be extremely slow (5 mg reduction every 2 weeks). The pregnant woman addicted to barbiturates or major tranquilizers along with opiates should be detoxified during her second trimester in a very specialized detoxification center.

3. The pregnant drug dependent woman should be evaluated in a hospital setting where a complete history and physical examination, including laboratory testing, can be done to evaluate her overall health status.

4. Psychosocial counseling should be given by experienced social workers aware of the medical, as well as social and psychological, needs of this population.

5. Mother-infant attachment should be encouraged prenatally and after delivery. Enhancement of these women's parenting skills should be especially emphasized in an effort to decrease the possibility of child neglect.

6. Social and medical support should not end in the hospital setting; rather, outreach programs incorporating public health nurses and community workers should be established.

7. The ability of the mother to care for the infant should be assessed after discharge from the hospital by frequent observations in the home and clinic.

8. Mechanisms for following and supervising the infant's course after discharge from the hospital should be assured.

Research

Investigators should:

1. Study the effects of heroin and methadone on the pregnant addict's lifestyle by collecting socially and medically valuable data.

2. Investigate newer treatment modalities for the drug dependent mother (e.g., assess the safety of various methadone maintenance dosage regimens for the fetus).

3. Study the dietary habits and nutritional status of pregnant addicts, and compare findings with those in control groups of nonaddicted patients.

4. Evaluate mothering practices of women who have abused drugs during pregnancy and thus assess these individuals' ability to carry out a child-rearing role.

5. Develop "outreach" mechanisms so that more mothers and infants may be followed up. Doing so should provide a large enough experimental sample for appropriate statistical analysis, as well as appropriate control groups.

Clinicians must continue to strive for excellence in the care of pregnant drug dependent women and their children. Government agencies must realize their responsibility for these women and children and to society, and provide adequate planning and financial assistance for comprehensive services. If we do not begin to address certain issues in this population regarding prevention as well as treatment, we can expect the increasing number of female addicts to lead to an increasing need for custodial facilities for their potentially neurologically and psychologically handicapped children. The medical and custodial costs for these individuals are incalculable. Only if clinicians and the government consider appropriate care for pregnant drug dependent women and their children as worthy of professional concern, will we be able to cope with the potential physical and behavioral effects of narcotic drugs on the pregnant woman, the fetus, the newborn, and the child.

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CRITIQUE

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Dr. Loretta Finnegan has presented an extremely thorough and exhaustive summary of the world literature on the various reports of perinatal and developmental effects of methadone. In her paper, it is stated that malabsorption is common in narcotic addicts because of the prevalence of hepatic and pancreatic disease. Although many heroin addicts and methadone maintained patients have liver disease only, some alcoholic heroin addicts and methadone maintained patients may have chronic pancreatitis and secondary malabsorption. This latter problem is in fact a relatively rare complication seen in the addict population. But rather than spend time on a few minor details, I think it would be more helpful to focus on the difficulties in studying the effects of opioids in the perinatal period in man.

The effects of opioids on the human reproductive system and especially on prenatal and perinatal development are extremely difficult to evaluate in studies in animals and in man for three major reasons and innumerable minor ones. These reasons will be detailed in this discussion. In spite of these inherent difficulties, the scientific and especially the lay literature is full of articles on these topics, many of which totally fail to be self-critical and also state various observations as unqualified facts. It is this very diffuse and uneven literature that all of us must draw upon, when given the task of assessing what is known and not known about the effects of methadone in the perinatal period. The literature contains apparent contradictions, which often lead to confusion and misinterpretation, especially when observations made in animal models are extrapolated to man.

The first major difficulty which is encountered when clinical studies of the effects of opioids in the perinatal period are attempted is that ethical constraints preclude the administration of any narcotics solely for

research purposes, except when compelling factors of need for information of specific types override the concerns of possible hazards.

Although many women as well as men may receive single or limited numbers of doses of a narcotic for the relief of pain, the medical indications which cause the pain will probably per se alter endocrine function and other related physiological systems. Normal physiology is also significantly altered during pregnancy. These alterations include a variety of changes in hepatic function, and changes in plasma protein content, both of which could significantly alter opioid disposition and effects. Endocrine function also is significantly altered during pregnancy (Kreek et al. 1967a; Kreek et al. 1967b; Kreek and Sleisenger 1970; Kreek 1973; Cushman and Kreek 1974; Kreek 1978; Kreek et al. 1980; Kreek 1981). Profound species differences exist with respect to the effects of pregnancy in each of these systems. Women in labor may receive limited numbers of doses of an opioid during labor and delivery, and certainly the disposition and effects on mother and child of a narcotic given in this setting can and should be studied, as has recently been done in the case of meperidine. However, it is now well recognized that the effects of an opioid when administered on an acute or subacute basis to a naive or subtolerant individual are distinctly different from the effects of an opioid administered on a chronic basis to a tolerant and dependent subject such as a woman in methadone maintenance treatment for addiction. Obviously opioids may not be administered on a chronic basis for the sole purpose of clinical investigation.

Studies carried out in heroin addicts are confounded by the fact that the amounts and dosing schedules of heroin self-administration remain unknown, as do exactly what other substances are being used or abused, either purposely or accidentally. Also, even if heroin could be studied in a clinical investigation setting to determine its effects in the perinatal period, heroin is a short-acting narcotic, and its pharmacokinetic properties are distinctly different than those of long-acting opioids, such as methadone, which is a drug now most commonly used in the maintenance treatment of addiction. Thus, even if the dosing schedules of the administration of the short-acting narcotic, heroin, could be controlled, with no other drugs or agents used during study, separate studies would be needed to determine the qualitative and quantitative effects of long-acting narcotics.

Methadone maintained patients could and should provide a more controlled group of potential study subjects for research, since the amount of opioid taken is known, the time of dosing may be controlled, and the general health status of such patients can be assessed. However, in any studies in this patient population, it must be recognized that 20 to 50 percent of methadone maintained patients use or abuse other drugs or agents, especially tranquilizers such as diazepam, and alcohol, and much larger percentages of patients use nicotine and caffeine. Thus, it is essential in any study, or even in broad surveys of effects of methadone on perinatal effects and postnatal development, that all patients be screened as carefully as possible with both history and existing technology to determine substances used and abused, that each subject be classified according to substance use and abuse, and that data analysis be carried out using appropriate subgroup analyses prior to any group analyses. These obvious, though all too frequently ignored, problems which complicate or even preclude interpretation of many otherwise careful clinical studies of the effects of methadone in the perinatal period and on perinatal development could be managed to an acceptable extent, although with considerable additional effort on the part of the investigators.

One could suggest that a simple solution would be to carry out such studies in animal models. When animal models are used, a second area of major difficulty is encountered. Although use of animal models, both in vivo and in vitro, will continue to provide an essential approach for delineating mechanisms underlying observations seen in man or whole animals, the use of animal models may be limited to that very important role. Physiological studies are often limited because of profound species differences, especially in reproductive biology. A more specific problem is that the pharmacokinetic properties of several opioids are profoundly different in various animal species as compared with man. Especially noteworthy is the fact that the opioid methadone, which is long-acting in man and has an apparent terminal halflife of 36-48 hours in man, has only a 90-minute halflife in the rat, one of the most commonly used experimental animals. During chronic daily dosing in man, steady plasma levels of active drug are achieved during most of the 24-hour dosing interval; no such steady state is achieved in animals unless a constant infusion, such as a mini-pump system, which has only recently been employed in any study, is used. Thus, the same effects of opioids

which are observed in the methadone maintained patients can only be emulated using a research design in animals in which some type of constant delivery system is used. Since this has not been done in most animal studies to date (and possibly cannot be done in chronic studies because of expense and technical difficulties), the animal studies which had been performed up to this point, and unfortunately also probably most which will be performed in the future, are really studies of effects of intermittent narcotism and abstinence, rather than of steady-state exposure to narcotics. Therefore there is no doubt that animal models, even in primates, cannot replace careful studies in man, especially with respect to elucidating the perinatal and developmental effects of methadone.

The third area of major difficulty in studies of the effects of opioids on reproductive function and on the perinatal period involves the analytical techniques available for such studies. It has only been in the last 5 to 10 years that sensitive and specific analytical techniques for the quantitative measurements of various opioids and their metabolites in blood, urine, feces, and tissues have been developed to the extent that rigorous studies relating to their disposition and effects can be conducted. Of course, such techniques are still being developed and refined, and to date there is only limited application of such technology to studies of the perinatal period in man.

One extremely exciting new research topic in this area is the interaction of exogenous opioids with endogenous opioids and their receptors. The analytical technology for quantitative measurement of the various endogenous opioids is still in the developmental stage and the major problem in specificity is the problem of cross-reactivity with other peptides which is inherent in many assays, along with the problem that exists of not being able to obtain the tissues or fluids necessary for analysis of specific endogenous opioids. The development of sensitive and specific assays for different peptide and steroid hormones involved in reproductive endocrine function in general and in the perinatal period specifically has really occurred during the last decade. Similar developments for study of the endogenous opioid systems will undoubtedly occur in the next decade.

Irrespective of the problems which result from these three major areas of difficulties and many other minor

ones, many provocative findings have been made concerning the disposition of narcotics in the perinatal period and their effects on the human fetus, the neonate, and child. Most of these Dr. Finnegan has reviewed in some detail. Further studies of methadone disposition in pregnant women are now being extended at this time and hopefully will provide some of the much-needed information concerning the actual amounts of drug which may be available to developing fetuses for action during this period. The studies carried out to date have suggested that even during steady-dose methadone treatment during the third trimester, plasma levels of methadone become progressively lower as the third trimester progresses, and that this lowering exceeds that which could be explained on the basis of increased body water and increased weight alone and has been shown not to be due to any changes in plasma protein binding of methadone (that is, binding to both albumin and globulin functions in humans). This lowering of plasma levels may well be due to increased tissue binding of methadone coupled with accelerated metabolism of methadone possibly due to the high levels of progestin present at that time.

Another very important area which has been studied and which would benefit by further studies is a more extensive and prolonged assessment of the amounts of methadone which pass in maternal milk to suckling neonate, and also studies to determine what may be the effects of either short-term (4 to 6 weeks) or long-term (longer than 6 weeks) nursing of a baby by methadone maintained mother. Contrary to a few erroneous reports, the amounts of methadone which are secreted into milk, and thus which can be ingested by neonates, are far too low to cause any type of "narcotic overdose" in the suckling neonates. The concentrations of methadone in maternal milk have been shown to be much too low to have any therapeutic value in the management of narcotic abstinence symptoms. It would seem that allowing methadone maintained mothers to nurse their babies would be safe and beneficial from both health and psychological standpoints. However, the possible physiological effects of the prolonged ingestion of even small amounts of methadone which would be received by neonates during nursing over several weeks to months of time have not yet been determined. Studies to date of methadone content in milk have been carried out only during the first few weeks postpartum. In these studies it has been shown that the amounts of methadone in milk are extremely low and would be much lower than a comparable dose of opiate given to a neonate requiring such a drug

for any medical indication. Further studies of the amounts of methadone which pass into milk after the first 2 weeks of nursing and also studies of any possible effects of nursing on the neonates are needed at this time.

One observation has been made in a mixed group of methadone maintained and heroin addict mothers, some of whom were also using street methadone. This is a finding of thrombocytosis in the neonate within a few days after birth. This clinical finding has been extended with respect to the numbers of patients studied and also with respect to the length of time that the neonates were followed after birth. It was shown that thrombocytosis may persist as long as 6 months in some of these children born of methadone maintained or heroin addict mothers. A laboratory study has been carried out using a mouse model in which use or abuse of other agents could be excluded. It was shown that chronic administration of methadone in the female mice before and during pregnancy resulted in an increase in platelets in the neonates following birth but not in the mother mice. It should be noted that increased platelet counts have never been observed in adults during chronic methadone maintenance treatment. In the mouse model study as in the human neonate study, it was shown that thrombocytosis persisted for a prolonged time but then remitted spontaneously. In both the clinical studies and in the animal model, this thrombocytosis was not associated with any clinical symptomatology. However, different types of adverse reactions, which might be complications of thrombocytosis, might be postulated. It is of special importance in consideration in animal models, however, to ask the question whether or not thrombocytosis was due to a narcotic effect or narcotic abstinence effect. In the experimental design used, methadone was administered only once a day in the mouse, and halflife of methadone in the mouse was shown to be less than 110 minutes. Thus, during every 24-hour dosing interval, each animal underwent episodes of narcotic effects and also of narcotic abstinence effects. Similarly, in most of the human mothers maintained on methadone, doses of methadone are reduced during late pregnancy. This, coupled with the now documented lowering of plasma levels during late pregnancy during steady dosing, would suggest that the human neonate *in utero* also would experience intermittent episodes of narcotic effects and narcotic withdrawal effects. A similar situation would pertain in the fetuses of heroin addicted pregnant women. Thus, it is not clear whether the thrombocytosis effect is due to narcotic or to narcotic withdrawal.

This same question exists with respect to determining the etiology of many other observed physiological and pathological effects attributed to narcotics per se in neonates born of heroin addict and/or methadone maintained mothers. Dr. Finnegan has discussed several of these observations in her detailed discussion. It is important to stress that studies need to be designed to determine the relative role of narcotic and narcotic withdrawal on a variety of effects observed in man as well as in animals.

Clearly the area of consideration of perinatal and developmental effects of methadone is a critical one. Well controlled small clinical studies in which multiple factors can either be controlled or delineated for subgroup analysis should be encouraged and supported at this time. Also longitudinal studies of small groups of well selected patients should be carried out. Emphasis should be made first on identifying and studying methadone maintained women who are pregnant and who are not polydrug abusers or alcohol abusers so that the effects of methadone per se can be determined. Then in later studies it would be desirable to determine what the effects of use or abuse of other drugs or alcohol may be. Such studies must be considered of secondary importance at this time, however, until the effects of narcotic per se and of narcotic withdrawal have been delineated. Emphasis should be placed on small excellent studies rather than huge surveys in which minimal to no assessment of health status and substance use and abuse of subjects is included and which thus may simply contribute more to the confusion of the literature.

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DISCUSSION SUMMARY

Barbara Gastel, M.D., and Thomas E. Collins

Major themes of this discussion included the treatment of the neonatal abstinence syndrome, mother-infant interaction, and the need for research on many other topics.

Several participants discussed the treatment of the neonatal narcotic abstinence syndrome. Dr. Finnegan began the session by noting that various drugs are now used to treat this condition and then mentioning that she is conducting a study comparing the efficacy of paregoric, phenobarbital, and diazepam for this indication. To date, in all studies, paregoric, an opiate, has been shown to be the treatment of choice. Dr. Kleber said that he has successfully used clonidine to treat the syndrome in five neonates. However, Drs. Finnegan, Kreek, and Sparber urged caution because this drug is a potent hypotensive and psychoactive agent in both humans and in animals and has caused adverse reactions in adult humans. Various participants agreed that methadone itself might be the logical agent to use, and suggested exploring the possibility of performing a well controlled study using methadone. Dr. Finnegan emphasized that the neonatal abstinence syndrome in infants of methadone maintained women is a benign, effectively treatable condition--especially compared to the many severe problems in newborns of heroin addicts.

Dr. Finnegan presented her impression that a large proportion of infants born to methadone maintained women have eye problems such as strabismus and myopia. A well designed, well controlled study of maternal methadone use and its effects on the eyes of offspring was identified as a high priority.

The interaction between methadone exposed infants and their parents also was of concern to the participants. Dr. Finnegan mentioned that infants' intolerance to holding (and thus lack of cuddliness) during methadone withdrawal could interfere with parent-child bonding or with the developing relationship between parent and child. In this context, Dr. Slotkin suggested that in offspring of methadone maintained women, growth retardation might result from the same mechanism as in the failure to thrive syndrome: insufficient and inappropriate

handling leading to abnormally low levels of growth hormone. Whether this is an environmental and sociocultural effect independent of methadone needs to be addressed. At the present time, Dr. Tove Rosen is studying the effects of methadone on methadone maintained mothers' offspring. She has two comparison groups, one from the same socioeconomic neighborhood not using narcotics, and one from a higher socioeconomic neighborhood, also not using narcotics. According to Dr. Ginzburg, preliminary findings seem to suggest that the differences found in the offspring in question are due more to socioeconomic status than drug use. Apparently, this is the only prospective study currently underway which attempts to identify the relative effect of parental drug use patterns and socioeconomic status on their offspring's growth and development.

Dr. Kreek proposed monitoring the fetal sheep both internally and externally during constant infusion of methadone to asess such variables as heart rate, respiratory rate, and fetal movement. However, Dr. Kreek also warned about overinterpretation of data in any animal species with respect to possible relevance to man since profound species differences exist, e.g., marked differences in plasma protein binding of methadone in humans as compared to the ewe, leading to inadvertent incorrect extrapolations of disposition and pharmacokinetic data with respect to man. Marked differences exist between pharmacokinetics, pathways of metabolism and routes of excretion of methadone in rodents as compared to man. Also, pharmacodynamic and "adverse reaction" data in animals should be interpreted with caution since near lethal (or lethal) doses of narcotics are often used; thus many studies are toxicological and not pharmacological. Topics identified for additional research included head circumference and rates of development in offspring of methadone maintained women.

CHAPTER 5. HEALTH CONSEQUENCES ASSOCIATED WITH THE USE OF METHADONE

Mary Jeanne Kreek, M.D.

The acute effects of any opioid in a naive individual are significantly different from chronic effects of opioids, since during chronic usage of any opioid, tolerance develops to most, but not all, various specific opioid effects. Also the effects of a short-acting narcotic, such as heroin or morphine, during chronic administration are, in part, both qualitatively and quantitatively different from those of a long-acting narcotic, such as methadone or LAAM, during chronic usage. This is because of the profound dispositional and pharmacokinetic differences between these two types of exogenous opioids. Whereas the duration of action of heroin during chronic usage is only 6-8 hours, the duration of methadone during chronic usage is 24-36 hours. As discussed in detail in a previous chapter, the plasma terminal halflife of methadone has been shown to be around 24 hours when no tracer technology is used in measuring plasma levels, and around 36-48 hours when stable isotope tracer methods are used to determine the fate of a single dose of methadone (Inturrisi and Verebely 1972; Kreek 1973b; Hachey et al. 1977; Kreek et al. 1978; Rubenstein et al. 1978; Kreek et al. 1979; Anggard et al. 1979; Nakamura et al. 1982). During chronic oral administration of methadone, there are minimal to no peak effects coincident with low peak plasma levels of methadone, which are usually less than twice the trough plasma levels; stable effects are observed coincident with relatively steady-state sustained plasma levels of drug during the remainder of the 24-hour dosing interval.

Diverse acute effects of narcotics have been known for years; they include effects on multiple organ systems. Of interest, since the discovery of a specific opiate receptor in 1973, more recently expanded to the discovery of multiple opiate receptors, and also the finding of multiple endogenous opioid ligands which bind at these receptors, it has been shown that many of the well known acute exogenous opiate effects in animals may be reproduced by administration of very large amounts of these various endogenous opioids. The specificity which endogenous opioids may have in producing various effects and also the

specificity of receptors for each of these individual opiate effects have yet to be fully elucidated. It has been shown that tolerance develops with respect to some of these acute opiate effects when large amounts of an endogenous opioid are repeatedly administered. Similarly, observations made in prospective and retrospective studies of the effects of methadone in man, that is, in former heroin addicts undergoing chronic maintenance treatment, during which a new homeostasis is apparently achieved, have provided important clues as to the possible roles of endogenous opioids in normal physiology.

During the early phases (at one time referred to as "Phase I" and "Phase II") of methadone maintenance treatment of heroin addicts, which could be described as "subacute" treatment, while doses of methadone are being gradually increased and then stabilized, multiple so-called "side effects" have been observed. Many of these "side effects" are simply well documented acute narcotic effects to which full tolerance has not yet developed during the first 6 months of chronic methadone treatment; these include the primary narcotic effects of euphoria, drowsiness, and somnolence, nausea and vomiting, difficulty in urination, edema of the lower extremities, menstrual irregularities, sexual function problems, insomnia, constipation, and also excessive sweating (Dobbs 1971; Kreek 1972; Yaffe et al. 1973).

Similar findings were made during a short-term cycle of methadone administration in a research setting in which six drug free former heroin addicts, with undetermined degrees of residual tolerance, were placed on rapidly ascending doses of methadone, reaching 100 mg/day by the seventh week; this dose was then maintained for an additional 8 weeks until time of completion of the study observations (Martin et al. 1973). In this study, decreased levels of pulse, blood pressure, and respiratory rate, and increased levels of rectal temperatures were noted. Also observed were hemodilution and persistent edema (both effects probably related to the well documented acute narcotic effect of antidiuretic hormone release), as well as other signs and symptoms typical of those which have also been observed in treatment programs where doses of methadone during early treatment are raised at inappropriately rapid rates which exceed the rate of development of tolerance to the various well known acute narcotic effects. In our early research experience with methadone in 1964, similar adverse reactions were observed when doses of methadone were ascended at similar rates which, in retrospect,

were recognized as being far too rapid. These early observations led to the treatment recommendations that for patients entering methadone maintenance treatment, usually directly from street addiction with heroin, the degree of tolerance and dependence be estimated, appropriate initial doses of methadone be given, and that most importantly, patients be carefully observed during the first several weeks of treatment. These recommendations stressed that individuals must be carefully observed during the first several weeks of treatment during which time stepwise increases of methadone doses are given, so that doses administered did not exceed the degree of tolerance which had been developed to the various acute narcotic effects. In early studies and also in our 6-year prospective followup studies, it became apparent that tolerance develops within 6 months to most acute and subacute narcotic effects, although tolerance develops even more slowly to some narcotic effects (Kreek 1975).

After 6 months or more of chronic methadone treatment, tolerance develops to many of these narcotic effects, and therefore most of the signs and symptoms disappear. In one study of patients in chronic treatment for 6 months or more, around 20-30 percent of patients continued to complain of problems related to both sleep and sexual function. Around 40 percent of patients complained of persistent constipation requiring laxative treatment. In our prospective study of the first consecutive 214 patients admitted to methadone maintenance treatment, who were followed from time of entry into treatment until after 3 years or more of chronic treatment, with daily doses of methadone ranging from 80-100 mg, abnormalities in sleep, in libido, or in sexual function persisted in only 10-20 percent of patients (Kreek 1972; Kreek 1973a; Kreek 1978; Kreek and Hartman 1982). Signs and symptoms of abnormalities in sexual function were not found to be correlated with abnormalities in sexual hormones levels or with fertility. The sleep abnormalities observed during chronic treatment were primarily those of insomnia rather than somnolence, which was observed only during the early months of treatment. Around 20 percent of patients maintained on methadone for 3 years or more continued to have chronic constipation requiring use of laxatives. The most frequently observed side effect of chronic methadone treatment was excessive sweating, experienced by around 50 percent of patients, but not resulting in any clinical problems, even in patients who carried out rigorous work or other exercise in a hot environment or in direct sunlight. Although tolerance develops to most of the acute

narcotic effects, tolerance does not develop to the primary desired effects of methadone as used in maintenance treatment; specifically, tolerance does not develop to the effects of methadone in preventing narcotic abstinence symptoms over a 24-hour dosing interval and also in preventing "drug hunger."

No significant signs and symptoms during chronic methadone treatment have been observed in other and more recent thorough evaluations of the medical status of patients in chronic treatment (Longwell et al. 1979; Kleber et al. 1980). Although it has been suggested that methadone treatment may cause obesity, very few cases of morbid obesity have been found within methadone-maintained patients. Weight gain certainly occurs in many heroin addicts entering chronic methadone maintenance treatment. However, although this might in part be due to some direct drug effects, lifestyle changes on entering treatment are dramatic and include increased food intake and a more sedentary existence. Therefore, the relative role of multiple factors resulting in any weight gain would be difficult to assess.

Chronic constipation must be regarded as a significant (and possibly the only significant) adverse medical complication of methadone treatment. In the 20 percent of patients in chronic treatment, constipation persists, and must be managed aggressively by proper use of laxatives, stool softeners, and diet. The only death reported due to methadone itself in chronic methadone-maintained patients receiving regular full treatment doses of drug is one death due to the complications of severe chronic constipation (Rubenstein and Wolff 1976). A methadone-maintained patient with chronic constipation consistently refused management of this problem and developed total obstipation with megacolon and ileus, again refused treatment, and eventually died of complications related to prolonged complete obstipation. Post-mortem examination confirmed this as a cause of death. This case underscores the need to manage chronic constipation in those patients in whom chronic constipation is a persistent opioid effect.

In addition to the one case of death due to constipation in methadone-maintained patients, there has been only one additional report of a serious adverse reaction, probably attributable to methadone itself. Although there have been numerous reports of neurotoxicity in animal studies in which usually very high doses of methadone were used (undoubtedly with resultant respiratory depression and

hypoxia), to date only one case of a neurological problem specifically linked to methadone maintenance treatment has been reported (Wasserman and Yahr 1980). The problem arose in a 25-year-old male patient with a 7-year history of narcotic addiction and polydrug abuse who had methadone maintenance treatment. After several months in methadone maintenance treatment, he developed symptoms of lightheadedness, dizziness, visual disturbances, speech disturbances, and tremulousness. Over a 2-month period these symptoms progressed to the development of choreic movements of the arms, shoulder, and head along with abnormal speech, with both stuttering and difficulties in verbalization. The patient was seen by a neurologist and it was decided to slowly reduce his methadone dose to zero dose, which was accomplished within 2 additional months. No other medications were administered to treat his problem; it is not known whether or not any observations of other drugs occurred during this period of time. His symptoms improved with disappearance of choreic movements and return of speech to normalcy following complete detoxification from methadone. He remained methadone free over the next 6 months with no return of choreic or speech defects. The authors of this report suggest that other cases similar to this may be seen in the future since it took many years of chronic treatment of large numbers of patients before movement disorders related to the neuroleptic medications were documented. However, although it is possible that additional cases of this type will be identified in patients receiving chronic methadone treatment, high dose chronic treatment has been used for 18 years with approximately 85,000 patients in treatment during each year since 1972 (thus approximately 1.5 million patient-years of treatment) and no other cases of neurotoxicity have been reported.

In the general health care management of methadone-maintained patients, it is important to recognize that during chronic methadone treatment, tolerance develops rapidly to all analgesic effects of methadone. Thus, it has been shown that these patients perceive noxious stimuli just as normal subjects and also drug free former addicts (Ho and Dole 1979). methadone-maintained patients experience suffering due to pain under the same circumstances, such as injury, surgery, and disease, as do otherwise normal subjects, and management of pain is necessary. Short-acting narcotics are the drugs of choice for the management of pain in methadone-maintained patients. Because of the degree of tolerance which has developed in these patients, higher doses and usually more frequent doses of short-

acting narcotics are required, since effectiveness of these drugs will be limited to that interval of time when peak plasma levels of short-acting narcotics exceed the degree of tolerance which has been developed. It should also be stressed that pentazocine (Talwin) is contraindicated in methadone-maintained patients because this drug has both agonist-antagonist actions and will precipitate narcotic abstinence symptoms in narcotic tolerant and dependent individuals.

In several prospective and retrospective studies, it has been shown that 50-60 percent of heroin addicts and patients entering methadone maintenance treatment have biochemical evidence of chronic liver disease, and that over 50 percent of former heroin addicts in chronic methadone treatment or in drug free environment treatment have persistent abnormalities of liver tests (Cherubin 1967; Jersild et al. 1970; Cherubin et al. 1970; Kreek 1972; Kreek et al. 1972; Cherubin et al. 1972a; Cherubin et al. 1972b; Stimmel et al. 1972; Martin et al. 1973; Kreek 1973a; Kreek 1973c; Stimmel et al. 1973; Cherubin et al. 1976; Sapira 1977; Kreek 1978; Kreek and Hartman 1982). However, in both prospective and retrospective studies, there has been no evidence of any hepatoxicity due to methadone itself (Kreek et al. 1972; Kreek 1973a). Patients with normal liver function at time of admission to methadone treatment do not develop abnormalities of liver function during chronic treatment except when alcohol is used to excess or acute viral hepatitis occurs (Kreek et al. 1972; Kreek 1973a). Also, in these patients with hepatic abnormalities at admission, deterioration does not occur except in patients using excessive amounts of alcohol. However, persistent abnormalities in liver function have been observed in patients receiving chronic methadone treatment for 6 years or more and in these patients there is very rare parenteral use of any drugs.

The etiology of chronic liver disease observed in methadone-maintained patients is primarily of two types: sequelae of earlier acute infection with hepatitis B virus or one of the non-A non-B viruses, or types of alcohol related liver disease (Cherubin 1967; Cherubin et al. 1970; Cherubin et al. 1972a; Cherubin et al. 1972b; Kreek et al. 1972; Stimmel et al. 1972; Kreek 1973a; Stimmel et al. 1973; Cherubin et al. 1976; Kreek 1978; Kleber et al. 1980). Six to 12 percent of adults and adolescents in methadone maintenance have been shown to be carriers of hepatitis B antigen. This is a ten- to twentyfold greater prevalence than exists in the general population. Also it

has been shown that 50-60 percent of all methadone-maintained patients have hepatitis B core antibody, thus documenting a previous clinical or subclinical episode of hepatitis (Stimmel et al. 1972; Kreek 1973a; Kreek 1978; Kleber et al. 1980). In a study of methadone-maintained patients all with clinically demonstrable liver disease, 96 percent have some marker of previous hepatitis B infection (Novick et al. 1981). The percentage of patients with sequelae due to non-A non-B viruses is unknown.

In clinical studies from this laboratory as well as from others, it has been shown that approximately 25-35 percent of adult and adolescent methadone-maintained patients are chronic abusers of alcohol and that about 20 percent of street heroin addicts have a similar problem of alcohol abuse. It is in this subgroup of patients who use alcohol to excess that progressive liver disease is observed during chronic methadone treatment (Kreek et al. 1972; Kreek 1973a; Kreek 1973c; Kreek 1978; Beverley et al. 1980, Hartman et al. 1983, in press).

Overt adverse medical consequences resulting from chronic methadone treatment are thus for the most part limited to a few mild signs and symptoms and these occur in less than 20 percent of patients, with the exception of increased sweating which occurs in around 50 percent of patients. Serious toxic reactions are extremely rare (Kreek and Hartman 1982). However, numerous biochemical and physiological alterations have been observed during acute and subacute methadone treatment and some of these alterations have been shown to persist during chronic methadone treatment. These signs are of interest from the standpoint of increasing our understanding of the physiological characteristics of the tolerance and dependent state in man and also of understanding which narcotic effects may persist without the development of tolerance; this may in turn give insight into which aspects of normal physiology may be at least in part under the control of the various endogenous opiates, the endorphins, dynorphins and enkephalins.

Effects of methadone on respiratory physiology have been studied by four independent groups. In a study of 96 methadone-maintained patients in treatment from zero to 61 months, with a mean of 12 months, 30 percent had some pulmonary function abnormalities which were mild and asymptomatic (Kleber et al. 1980). Primarily these abnormalities consisted of increases in flow rates, and very

mildly restricted pulmonary function patterns. In a followup study of 32 of these patients, with a mean of 11 months of further methadone treatment, there was a trend toward a slight improvement in pulmonary function, with no deterioration observed. Thus, there was no evidence that methadone caused any of these abnormalities, although it is possible that in these patients in whom tolerance had not yet developed to acute effects on the respiratory system, methadone could have contributed to the abnormalities observed. Of great importance, there was no evidence that methadone resulted in any deterioration of these early abnormalities; rather, improvement was observed as length of time in treatment increased. It should be emphasized that in this study, 90.6 percent of patients were long-term cigarette smokers. It was felt by the clinical investigators carrying out this study that changes in pulmonary function observed might be due to cigarette smoking, and might also be due to former intravenous use of heroin containing foreign materials which might have caused mild, pulmonary embolic disease (Kleber et al. 1980).

In other studies, several alterations in normal respiratory physiology have been observed during early methadone maintenance treatment, but tolerance has been demonstrated to develop to all but one of these alterations during chronic long-term treatment (Marks and Goldring 1973; Santigo et al. 1977). The early alterations observed include decreased sensitivity of the central nervous system receptors to carbon dioxide, alveolar hypoventilation, and arterial hypercapnia. However, only one alteration in normal respiratory physiology observed during the early period of methadone treatment has been shown to persist during chronic treatment of 12 months or more; this is a decreased sensitivity of central nervous system receptors to hypoxia (Santigo et al. 1977). In the clinical literature to date there have been no clinical case reports or observations of clinical symptoms referable to this particular alteration in pulmonary physiology. Recently, it has been shown that normal hyperventilation of late pregnancy is diminished in methadone-maintained pregnant women (Metcalfe et al. 1980). However, any possible clinical correlates of this finding or implications for fetal physiology have not been elucidated. Of great interest, it has recently been shown that endogenous opioids may play a role in normal pulmonary physiology.

In a prospective study of 214 patients followed from time of admission to methadone treatment for a minimum of 3-6

years thereafter, no signs or symptoms referable to the cardiovascular system were noted on specific questioning and no abnormalities in physical examination or in electrocardiograms were observed during chronic treatment (Kreek 1972; Kreek 1973A). In a recently reported study of specific aspects of cardiovascular physiology, some abnormalities of phonocardiogram tracings and electrocardiogram tracings were observed in a group of 200 asymptomatic patients in methadone treatment for 2 months to 5 years (Kleber et al. 1980). The abnormalities observed included the presence of S_4 gallop after exercise in 30 percent of patients, suggesting some abnormalities of compliance of the left ventricle after exercise, and electrocardiogram findings suggestive of possibly depressed left ventricular ejection function in 47 percent of patients. No symptoms were delineated. No attempt was made in this study to exclude alcohol abusing subjects or subjects with other types of polydrug abuse. However, it was shown that there was no correlation between the presence of these abnormalities and either the duration of methadone maintenance treatment or the dose of methadone received. Thus, there was no evidence that the alternations observed were due to methadone but rather more likely were due to cardiac insults sustained during chronic parenteral heroin abuse prior to entering methadone maintenance treatment.

Assessment of renal function in methadone-maintained patients has been carried out in several studies (Kreek 1972; Kreek 1973a; Kleber et al. 1980). Pyuria has been observed in around 20 percent of patients at time of admission to methadone treatment, with the percentage of patients with this problem decreasing with time in treatment. Proteinuria has been observed in around 10 percent of patients at time of admission to methadone treatment. Blood urea nitrogen levels, which in a large prospective study were found to be elevated in over 20 percent of heroin addicts at time of admission to methadone maintenance treatment, returned to normal levels in a significant number of methadone-maintained patients after 3 or more years of chronic methadone treatment. Therefore, there is no evidence that methadone is nephrotoxic.

Ophthalmological evaluation has been carried out systematically in 85 methadone-maintained patients in treatment for 2 months to 4 years (Kleber et al. 1980). The only abnormality found in an unexpectedly increased percentage of patients for the age of the study group was the finding of borderline or slightly elevated intraocular pressures in 18 percent of patients studied. However, there was no

correlation between this isolated finding and either the duration of time in methadone treatment or the methadone dose. The patients with this finding were asymptomatic. Also, in a follow-up ophthalmological examination of 20 patients, there was no change in intraocular pressure during increasing time in methadone treatment.

Hematological indices have been measured in several studies of patients in chronic methadone treatment. In the largest prospective study of 214 patients and the largest retrospective study of 1,435 patients, there was no evidence that methadone was a toxic agent for the hematologic system. Elevated percentages and also absolute numbers of polymorphonuclear leukocytes were observed in heroin addicts entering methadone maintenance treatment; however, it was shown that these abnormalities return to normalcy during 3 or more years of chronic methadone treatment (Kreek 1973a).

Neurological assessment and also performance assessment of methadone-maintained patients during chronic treatment have not revealed any abnormalities which could possibly be attributable to methadone treatment (Gordon and Appel 1972; Lenn et al. 1975-76; Appel and Gordon 1973).

A variety of laboratory test abnormalities and also biochemical abnormalities have been observed in patients during chronic methadone maintenance treatment. Serum protein and immunological abnormalities have been observed in patients during long-term methadone treatment which may be in part due to chronic liver disease, and in part to a long past history of chronic injection of foreign substances along with heroin prior to entering methadone treatment (Kreek 1972; Sherwood et al. 1972; Kreek 1973a; Geller and Stimmel 1973; Cushman 1973a; Cushman 1973b; Cushman and Grieco 1973; Cushman and Sherman 1974; Drusin et al. 1974; Cushman et al. 1977). To date, only one of these alterations, increased albumin synthesis, has been shown to be due to opioid administration (Kreek et al. 1972; Rothschild et al. 1976). However, other drug related or unrelated factors altering some aspects of immune response or protein systhesis may also be involved in the abnormalities observed. Elevated levels of total serum protein, serum albumin, and total globulin fractions as well as elevations in specific globulin fractions including α_2 globulins and gamma globulins along with elevated levels of immunoglobulins IgM and IgG have been observed during chronic treatment (Kreek et al. 1972). Biological false positive test results for syphilis have

been frequently observed and are related to elevated IgM levels. Thyroid binding globulin levels are also elevated in methadone-maintained patients leading to apparent elevations in T_4 levels without any evidence of altered thyroid function (Shenkman et al. 1972; Webster et al. 1973; Azizi et al. 1974; Bastomsky and Dent 1976). Lymphocytosis is observed in around 20 percent of patients entering methadone treatment and also in patients after 3 or more years of chronic long-term methadone treatment (Kreek 1972; Kreek 1973a). Abnormal percentages of B cells and abnormal T cell rosette formation have been reported. Some of these alterations in immune function may be due to direct or indirect opioid effects.

In both our prospective and retrospective studies of the physiological effects of chronic methadone treatment, we have observed normal to elevated levels of serum albumin in patients at time of admission to methadone treatment and even greater numbers of patients with elevated levels of serum albumin after 3 or more years of chronic methadone treatment (Kreek 1972; Kreek et al. 1972; Kreek 1973a; Kreek 1978). These findings of persistently upper normal to increased levels of serum albumin are very provocative, especially in this patient population since there is a high prevalence of chronic liver disease and also alcohol abuse, both of which are associated with lowered levels of serum albumin. Also at time of admission to methadone treatment, the nutritional status of many patients is lower than normal. Usually serum albumin levels have a reciprocal relationship with serum globulin levels, but this has not been found to be the case in methadone-maintained patients. There is no precedent for any clinical condition or drug administration resulting in sustained elevation in serum albumin levels, although transient increases in levels have been observed in a variety of settings. In subsequent studies of both adult patients and also adolescent methadone-maintained patients, similar findings of elevated levels of serum albumin have been made (Kreek 1978). Also similar findings of normal to elevated levels of serum albumin have been made in special studies of alcohol abusing methadone-maintained patients (Beverley et al. 1980; Hartman et al. 1983).

To determine whether the exogenous opioid methadone itself may significantly alter albumin disposition, studies of albumin distribution and metabolism have been carried out in rabbits using specially tested lots of ^{125}I rabbit albumin (Rothschild et al. 1976). Albumin disposition was

studied in animals before and after chronic methadone administration (4 mg/kg body weight/day for 3 months). Several changes in albumin disposition were observed including increased total exchangeable albumin, increased serum albumin levels, increased total extravascular albumin levels, and increased rather than decreased rates of albumin degradation. Thus, using the whole rabbit model, there is experimental evidence that chronic methadone administration results in sustained net increase in albumin synthesis.

It has been demonstrated in numerous studies that the acute administration of short- and long-acting narcotics, or of large amounts of endogenous opioids, cause various significant biochemical alterations in normal endocrine and neuroendocrine function. Tolerance develops to most of these neuroendocrine effects during chronic methadone treatment in most patients. Many findings concerning the acute effects of opioids in endocrine function which are made using animal models cannot be extrapolated directly to man, because in animals the pharmacokinetic properties of most narcotic drugs are significantly different than in man. The plasma apparent terminal halflife of methadone during chronic oral administration in man is 24 hours when conventional techniques of analysis are used, and has recently been shown to be much longer, approximately 36-48 hours, when the more sensitive stable isotope tracer techniques are used (Inturrisi and Verebely 1972; Kreek 1973b; Hachey et al. 1977; Kreek et al. 1979; Nakamura et al. 1982). However, the plasma apparent terminal halflife of methadone in the rat during chronic administration is 90 minutes (Kreek 1979a). Also of importance in trying to interpret several of the conflicting reports concerning the endocrine and neuroendocrine effects of methadone treatment in man, it is crucial to appreciate the fact that even in the apparently well executed studies of endocrine function, it is not always clear whether or not methadone-maintained patients with liver disease and also those patients using alcohol or marijuana on a regular basis have been excluded, and such factors can significantly alter endocrine function.

In several studies of methadone-maintained patients, workers have found that plasma levels of FSH and LH may be significantly reduced in some patients during the first 6-12 months of methadone treatment, and that feedback control of release of trophic hormones is altered during early treatment. However, when the same patients are followed sequentially in a prospective study design or

when studies are carried out in patients stabilized on chronic methadone treatment for 1 year or more, FSH and LH levels and patterns of release have returned to normal (Kreek 1972; Martin et al. 1973; Kreek 1973a; Cushman and Kreek 1974a; Cushman and Kreek 1974b; Santen 1974; Santen et al. 1975; Gordis and Kreek 1977; Kreek 1978; Kreek 1979a). Although a very large proportion, up to 90 percent, of female heroin addicts have either very irregular menses or secondary amenorrhea, after 1 year or more of chronic methadone treatment, it has been shown that menses returned to normal in essentially all premenopausal patients and that these patients become fertile (Blinick 1968; Kreek 1972; Kreek 1973a; Santen 1974; Santen et al. 1975). In special studies of reproductive endocrinology in female methadone-maintained patients, it has been shown that although various biochemical indices are abnormal during the first several months of methadone treatment, especially the positive feedback control by estrogens of LH release, these abnormalities return to normal as tolerance develops during chronic treatment of longer duration (Martin et al. 1973; Santen 1974; Santen et al. 1975).

However, a few alterations in indices of reproductive endocrinology remain abnormal in some patients in chronic methadone maintenance treatment for longer than 1 year. There have been several studies in which plasma levels of testosterone have been measured during acute or subacute treatment with methadone, but only a few such studies have been carried out in patients maintained on chronic methadone treatment for 1 year or more (Cushman 1973c; Cushman and Kreek 1974a; Cushman and Kreek 1974b; Mendelson et al. 1975a; Mendelson et al. 1975b; Cicero et al. 1975; Gordis and Kreek 1977). In several published reports, it is not clear whether or not patients with chronic liver disease or who use alcohol or marijuana were excluded; in some studies it is clear that they were not excluded according to the statements made concerning study subject selection, and in none of the reported studies was subgroup analysis carried out to determine whether or not differences exist in special subgroups of patients. Also control groups for the various reported studies were usually drawn from students, laboratory workers, or other medical personnel. Such study subjects cannot be considered to be appropriately matched controls for the former heroin addict methadone-maintained patients. Another major problem in studies reported is that since a variety of laboratory methods have been used for hormone assays, quality control for assays performed has varied and a wide range of values for each hormone has been accepted as being "normal." All of

these problems made it very difficult to interpret the various reports concerning the effects of methadone on reproductive endocrine function. In some of these reports it has been stated that from 15-55 percent of methadone-maintained patients have lower than normal plasma levels of testosterone (Cushman 1973; Cushman and Kreek 1974a; Mendelson et al. 1975a; Cicero et al. 1975). In one study of male patients in treatment for 1 year or more, testosterone levels were reported to be normal in patients receiving up to 60 mg/day of methadone (Mendelson et al. 1975a). However, in 14 patients receiving from 80-150 mg/day of methadone, four patients had testosterone levels of less than 300 μg/ml, a level often described as the lower limit of normal. In another study in which plasma levels of methadone and testosterone as well as LH were both measured in samples of blood obtained at sequential time-points following oral dosing with methadone in maintained patients, lowered levels of testosterone were observed in six of 43 determinations (Cushman and Kreek 1974a). However, the concomitant plasma methadone levels range from 0.10 to 0.75 μg/ml and the LH levels were normal in all patients in whom lowered testosterone levels were observed (Cushman and Kreek 1974a). Thus, it was difficult to relate either dose or plasma level of methadone clearly to plasma levels of testosterone. In one study, which included 26 patients maintained on methadone for 3 months or more, each receiving at least 25 mg/day of methadone, various indices of function of male sex organs were measured (Cicero et al. 1975). In this report it was stated that one criterion for selection of study subjects was "absence of frequent use of drugs other than aspirin, nicotine, caffeine, alcohol, or marijuana." Thus, it should be inferred that some patients were using alcohol and/or marijuana regularly; also, exclusion criteria did not include the presence of chronic liver disease and thus patients with chronic liver disease of various types may have been included in this study. In this study it was shown that ejaculate volume was reduced in methadone-maintained subjects and that when sexual abstinence had been observed for more than 3 days, sperm count was significantly higher in methadone-maintained patients than in control subjects (Cicero et al. 1975). Sperm motility was measured in only a very small number of patients and although the motility appeared to be reduced in some of the methadone-maintained subjects, the number of determinations made were too few for this finding to be interpretable. Clearly, further careful studies in well selected and characterized patients in chronic methadone maintenance treatment including subgroups of patients who

are otherwise healthy, patients with chronic liver disease, and patients known to chronically use moderate and large amounts of alcohol and marijuana should be studied with data analyses for each subgroup carried out to determine any possible effects of chronic methadone maintenance treatment on reproductive endocrine function and sex organ function.

It has been well documented that the acute or subacute administration of narcotics to humans results in a predictable significant reduction in plasma cortisol levels presumably reflecting a reduction of ACTH levels and that during cycles of subacute or chronic morphine administration in former heroin addicts, both cortisol levels and total urinary excretion of glucocorticoids are reduced. During chronic long-term methadone administration, our group and others have shown that plasma cortisol levels are within range with a brisk but normal circadian variation (Cushman et al. 1970; Kreek 1972; Renault et al. 1972; Kreek 1973a; Cushman and Kreek 1974b; Kreek et al. 1981b). In recent studies we have also shown that plasma levels of ACTH are normal in patients during chronic long-term methadone maintenance treatment (Kreek et al. 1981b). In early studies reported in 1972 and 1974, we have found that during the first 2 months of chronic methadone treatment, significant alterations of function of the hypothalamic-pituitary adrenal axis do exist, as evidenced by abnormal metyrapone test results, indicating reduced hypothalamic-pituitary reserve for release of tropic hormones (Kreek 1972; Cushman and Kreek 1974b). We also showed tolerance develops to this interesting effect after 3 or more months of stabilized methadone treatment.

In 1977, we reported the very provocative findings of elevated levels of prolactin in significant percentages of methadone-maintained patients, a finding confirmed by other groups. In a highly controlled study of patients maintained on steady dose of methadone treatment for more than 1 year, the intriguing finding also was made of altered prolactin release, usually without but sometimes with absolute elevation in prolactin levels, with peak prolactin levels occuring at time of peak plasma levels of methadone; prolactin levels returned to a normal pattern of diurnal variation following detoxification from methadone (Kreek 1978; Kreek and Khuri 1979). These findings are of considerable interest in attempting to understand the mechanisms underlying the addictive disease process. Since prolactin is normally under tonic inhibitory control by dopaminergic factors, and possibly by dopamine itself,

the finding of persistent responsiveness of prolactin release to peak levels of opioids, during chronic methadone administration when tolerance has developed to most of the endocrine and neuroendocrine effects of opioids, is provocative, and suggests that even during long-term treatment, methadone may reduce, antagonize, or block central dopaminergic action.

We have performed studies to elucidate further the effects of chronic methadone treatment on prolactin release as well as on related peptide and steroid hormones in well classified subgroups of patients, including otherwise healthy subjects, patients with defined types of chronic liver disease, and patients receiving anticonvulsant treatment with phenobarbital and phenytoin, both of which have been shown to lower plasma levels of methadone (Kreek et al. 1976; Kreek and Khuri 1979). One methadone-maintained woman has been followed throughout a normal pregnancy with respect to the effects of methadone on prolactin release. All patients were studied in a metabolic research ward after several days of stabilization during which no other drugs were administered; normal day-night cycles were established, time of meals scheduled, and time of doses of methadone controlled. Blood specimens were drawn through intravenous catheters before (at 9 a.m.) and at 4 hours (1 p.m.) and 10 hours (7 p.m.) after oral administration of the daily dose of methadone. Plasma levels of methadone were determined by gas liquid chromatography techniques with peak levels of methadone as usual observed around 4 hours after the oral dose. In this group of otherwise healthy maintained patients, plasma levels of FSH and LH were within limits and there was a normal diurnal variation in levels. In these patients, peak plasma levels of prolactin occurred around 4 hours after the oral dose of methadone, the time when peak levels of methadone were also observed. Absolute levels of prolactin exceeded the upper limits of normal in only some patients. However, in all but one patient, the expected diurnal variation of prolactin levels (with highest levels in morning) was altered, with peak levels observed at 1 p.m., 4 hours after the methadone dose. Similar findings were made in patients with chronic liver disease and also in patients receiving anticonvulsant treatment, despite the fact that plasma levels of methadone were much lower in this group. In the one pregnant methadone-maintained patient, plasma levels of methadone were found to become progressively lower during the third trimester of pregnancy. Peak plasma levels of methadone continued to occur around 4 hours after oral dosing and peak plasma

levels of prolactin were also observed at that time, even in late pregnancy when prolactin levels were appropriately very high. This responsiveness of prolactin release to peak levels of methadone was thus observed in all subgroups of long-term methadone-maintained patients.

It has been reported that catechol estrogens, along with dopamine, may inhibit prolactin release, whereas estrogenic metabolites of estradiol may facilitate prolactin release. We have carried out studies to determine the effects of chronic methadone treatment on the formation of catechol estrogen (Kreek et al. 1981a). There were no differences in catechol estrogen formation in otherwise healthy methadone-maintained patients as compared with otherwise healthy unmedicated control subjects. Therefore it is unlikely that reduced peripheral formation of catechol estrogens is a mechanism underlying this observed phenomenon of persistent responsiveness of prolactin release to peak plasma levels of methadone.

In reported studies from other laboratories and our own, performed primarily in animals, chronic administration of exogenous opioids or their antagonists have been found either to have no effects on or to reduce brain or plasma concentrations of endogenous opioids. In recent studies carried out in the rat, we have shown that chronic administration of methadone (2.5 mg/kg x 30 days) did not alter levels of β-endorphin in any region of the brain, in the pituitary, or in the plasma (Ragavan et al. 1983, in press). However, chronic administration of the narcotic antagonist, naltrexone (2.0 mg/kg x 30 days or 4.9 mg/kg x 36 days), resulted in significantly depressed β-endorphin concentrations in the amygdala, thalamus, and hypothalamus, but not in the pituitary.

It is known that β-endorphin is derived from β-lipotropin and that β-lipotropin and ACTH share a common 31 K precursor. In a variety of studies carried out in animal models and in man, it has been shown the ACTH, β-lipotropin, and β-endorphin are released in parallel with each other under normal conditions and in stress. Many years ago we performed serial metyrapone studies in patients during the following induction into methadone maintenance treatment (Kreek 1972; Cushman and Kreek 1974b). In these early studies, metyrapone was administered in divided doses over a 24-hour period and response was determined by measurement of urinary excretion of 17-hydroxycorticosteroids, which normally rise two- and threefold in response to metyrapone administration because of the blockade of 11-B

hydroxylation which prevents the formation of cortisol by the adrenal cortex. This results in increases in production by the adrenal of the precursors of cortisol. During the first 2 months of methadone treatment, at a time when the doses of methadone were being increased and tolerance was developing to diverse narcotic effects, the response to metyrapone was significantly reduced, indicating suppressed production of corticotropin releasing factor or ACTH in response to chemically induced stress. However, when the same patients were restudied after 3 or more months of chronic methadone treatment, the response to metyrapone had become normal, with increased urinary excretion of 17-hydroxylated steroids indicating a normal release of increased amounts of corticotropin releasing factor and ACTH in response to stress.

We have recently completed an initial study to determine the effects of long-term administration of methadone on plasma levels of -endorphin and simultaneously on levels of ACTH and cortisol in man (Kreek et al. 1981b). Eight patients who had received methadone on a daily basis for 2 years or more were studied in a clinical research unit under controlled conditions detailed above. The lower limits of detection of -endorphin immunoreactivity with the radioimmunoassay used was 7 pg/ml. Plasma levels of -endorphin were undetectable in one-third of 24 otherwise control subjects and mean levels of -endorphin were undetectable in six to eight methadone-maintained patients at time 0, that is, 24 hours after the last dose of methadone, with levels of 19 and 22 pg/ml in the other two patients. At 4 hours after the methadone dose, around time of peak plasma levels of methadone, plasma levels of -endorphin were undetectable in three of seven patients with mean level of 11.3±2.3 (SEM) pg/ml in the rest. At 8 hours after the methadone dose, plasma levels of -endorphin were undetectable in four of seven methadone maintained patients with mean levels of 12.2±1.4 (SEM) pg/ml in the others. In this initial study, levels of -endorphin were not abnormally high in patients maintained on methadone. The levels of -endorphin were within normal limits, although -endorphin was undetectable in plasmas of several patients at each time-point, just as in otherwise healthy control subjects, in those patients with measurable levels of hormone. Methadone, when used on a chronic long-term basis, has no apparent effects on peripheral levels of -endorphin, according to the results of this initial study.

Plasma levels of ACTH were also determined in these patients using radioimmunoassay techniques. The mean plasma level of ACTH was 73.1±7.9(SEM) pg/ml time 0; 88.5±18.1 (SEM) pg/ml at 4 hours; and 84.2±20.7(SEM) pg/ml at 8 hours after methadone dose. All of these ACTH levels were within normal limits. Neither ACTH levels nor β-endorphin levels were significantly different at the three time-points studied. Plasma levels of cortisol were also measured simultaneously in these patients. At time 0, which was 9 a.m., the means plasma cortisol level was 18.3 mg/dl, at 4 hours the mean level was 6.8, and at 8 hours after methadone dose, 7.2 mg/dl. Thus, cortisol levels were within normal limits, and a normal and brisk circadian variation in these levels was observed.

To summarize what is known about chronic effects and thus medical consequences of chronic use of methadone, many interesting physiological and biochemical alterations occur, but there are minimal side effects that are clinically detectable in patients during chronic methadone maintenance treatment. Toxicity related to methadone during chronic treatment is extraordinarily rare.

The most important medical consequences of chronic methadone treatment, in fact, is the marked improvement in general health and nutritional status observed in patients as compared with their status at time of admission to treatment. Most medical complications observed in methadone-maintained patients are either related to ongoing pre-existing chronic disease, especially chronic liver disease, the onset of which occurred prior to entry into methadone treatment, or to coexisting new diseases or illnesses or to ongoing polydrug or alcohol abuse. Clearly the most common cause of serious medical complications in methadone-maintained patients both during the methadone maintenance treatment and also during and following detoxification is chronic alcohol abuse.

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CRITIQUE

Herbert D. Kleber, M.D.

In trying to examine the health consequences of methadone use, the appropriate comparison group is always an issue. In practically all the studies that Dr. Kreek reviewed, the methadone-maintained group consists of individuals not only on methadone, but 20 to 30 percent have serious problems with alcohol, and an additional substantial number drink at least moderate amounts; probably 90 to 95 percent smoke cigarettes; and an unspecified number use mild to moderate amounts of marijuana.

I stress these three drugs because they are ones that individuals on methadone are usually permitted to use without the program expelling them, with the possible exception of excessive use of alcohol. I did not even bother to mention drugs such as cocaine, barbiturates, or minor tranquilizers for which ongoing use could lead to expulsion from the program. Therefore, if the reports come up with abnormalities, it is hard to know whether they are related to methadone or to one of these other agents.

Ideally these studies should be done on individuals prior to entering methadone treatment and periodically throughout their maintenance period; no other drugs should be involved. However, research must be conducted within the constraints of the treatment setting, and we have to be satisfied with what we are able to obtain within these constraints. This often means looking at abnormalities present when patients start on methadone and seeing whether they get worse over time. If they do not, then the assumption is often made that they are due not to the methadone, but to some preexisting condition perhaps related to heroin or its mode of use. Such conclusions, of course, beg the question as to whether the chronic methadone use prevented the correction of the abnormalities. To determine that, one would need off-on studies, but, again, in this group of patients it is extraordinarily difficult to do these. When off methadone, many of them would simply be back on heroin with the likelihood that whatever caused the initial abnormalities might therefore still be present.

With those observations out of the way let us now turn to specific points discussed by Dr. Kreek. Overall, her review is an excellent, thorough, and comprehensive one,

and it is hard to find much fault with it. One reason is that much of the important work in the area has been done by Dr. Kreek and her associates, which puts her into the forefront of the field (Kreek et al. 1972; Kreek 1973; Kreek 1979).

As far as acute effects of methadone, I have nothing to add other than to raise a question concerning Dr. Kreek's statement that "tolerance does not develop to the ability of methadone to prevent drug hunger." It was not clear how she was defining "drug hunger." She was clearly not talking about withdrawal symptoms since she had mentioned that earlier in the sentence. Therefore, I had to assume that she was equating drug hunger with craving. Craving, as the work of Meyer and Mirin (Mirin et al. 1976) has demonstrated, is basically a function of perceived availability of the drug. It can be measured in two ways: either by an individual's subjective description of himself in the craving state or by his objective behavior--whether he goes out and uses narcotics. Using both of these criteria, it can be shown that individuals maintained on naltrexone, especially after the first few weeks, do not demonstrate drug hunger or craving either. Subjectively they do not define themselves in the craving state, and, objectively, they tend to have clean urines. Conversely, many patients on methadone, especially in lax programs, will continue to use heroin.

As far as the effect of chronic methadone maintenance on weight gain is concerned, I agree with Dr. Kreek that although weight gain often does occur, it cannot be simply ascribed to metabolic effects of methadone considering the other factors present, such as lifestyle changes and possibly increased food intake. I would have found it useful, however, if Dr. Kreek had elaborated more on the effects of methadone on blood sugar level and possibly glucose tolerance. Morphine acutely raises blood sugar. Clinically, we know that during withdrawal there seems to be a marked craving for sweets, and addicts will tell you that the sweets tend to ameliorate some of the withdrawal symptoms. One possible explanation for this may relate to the hypothesis that led us to try clonidine for narcotic withdrawal (Gold et al. 1978; Gold et al. 1979), namely that many of the withdrawal symptoms are due to noradrenergic hyperactivity. Such hyperactivity would be expected to produce hypoglycemia, and it is possible that eating sweets, conversely, would produce temporary hyperglycemia which could have the effect of diminishing noradrenergic output by feedback to the locus coereleus.

I do not know what effect chronic methadone use has on this complex area of blood sugar, but would be interested in Dr. Kreek's observations here.

As far as possible neurotoxic effects of methadone, I cannot comfortably agree with Dr. Kreek's observation that this is unlikely considering that there have been approximately 1 million patient years of treatment with methadone and only one case documented in the literature of choreic movement. This lack of report could be due either to a true failure of methadone to produce the problem; or to the fact that most methadone programs have relatively minimal physician coverage and slight signs of dyskinesia could be missed; or to the possibility that many patients are not truly maintained on methadone for a long period without interruption but instead cycle on and off. Such drug holidays may prevent the development of the disorder. In any event, in order to put our own mind at ease on this, we are currently engaged in giving the AIMS test, which is used to detect tardive dyskinesia, to approximately 300 of our methadone patients and hope to have the study completed within a few months and be able to report it. If the disorder is very uncommon, then even its absence in 300 patients will, of course, not be conclusive, but the fact we will have looked for it thoroughly in this number will, at least, be a first step in ruling out this disorder. It may be also that it is necessary for some preexisting condition to be present for the condition to occur since in the one case reported the patient had a history of concussion.

As far as methadone maintenance on the liver is concerned, I agree with Dr. Kreek's two key points that individuals who start methadone with normal liver function tests tend to stay that way, except if excessive alcohol use or acute viral hepatitis occurs. In those patients with abnormalities at intake, there does not seem to be deterioration except, again, related to excessive alcohol use. However, as I noted in my introduction, one is still left with the question of whether the persistence of hepatic abnormalities in any way relates to the maintenance. Miller and Bloomer (1980), the investigators in the recent New Haven study, suggest that the persistence of the lesion may relate to impaired T cell function, and it is at least conceivable that an altered immune response in these patients could modify the normal sequence of recovery from hepatitis infection. Currently there is insufficient evidence to either rule in or rule out this possibility, but it should be investigated.

As far as methadone's effect on the pulmonary system, our recent study, which Dr. Kreek cites, showing gradual improvement in the pulmonary function disturbances noted at admission, was an encouraging finding (Littner and Bouhuys 1980). That this occurred in the face of 91 percent of the patients smoking cigarettes was indeed remarkable. We also have not noted any clinical problems due to the one abnormality that may be due to methadone, namely a decreased sensitivity of the central nervous system receptors to hypoxia. One might speculate, however, that perhaps it contributes to the occasional fatal combination of methadone and excessive alcohol, since such deaths may be due to respiratory depression.

The effects of methadone maintenance on the cardiovascular system are similar to those on the hepatic system, namely, abnormalities tend to persist throughout the course of maintenance with no deterioration and no relationship to length of methadone use. Thus, although it is likely that the methadone per se did not cause these difficulties, it is again not possible to rule out that its chronic use prevents them from going away. Thirty percent of the patients in our study (Langou and Cohen 1980) had some abnormalities of compliance of the left ventricle after exercise, and 47 percent had EKG findings suggestive of depressed left ventricular ejection function. Drs. Langou and Cohen suggest that one way of studying these abnormalities is to have repeat sequential measurements of systolic time intervals using EKG, phonocardiogram, and carotid pulse tracing both during and after submaximal bicycle exercises. In addition, a limited number of participants who continue to show abnormality should be tested by additional measurements such as echocardiography and myocardial imaging. It is of course true, as Dr. Kreek points out, that these findings currently do not have any immediately apparent clinical relevance and could, in fact, be due to the contamination of the sample with other drug use.

As far as the renal system is concerned, again it appears that chronic methadone use is not nephrotoxic. The key findings from our study by Forest and Hong (1980) was of pyuria not associated with proteinuria. Again the finding does not worsen with time on methadone and seems, if anything, to improve. The possibility of persistent interstitial nephritis due to heroin injection, which has been noted in animal studies, could be investigated further by a controlled prospective study of urinalysis and renal

function tests in narcotic addicts before entering treatment with methadone.

Ophthalmologic studies done in New Haven again find no particular lesions due to methadone, although there was an unexpectedly increased percentage of patients having borderline or slightly elevated intraocular pressures (Walsh 1980). Patients were asymptomatic, and the increase did not worsen during increased time on methadone. A remarkable feature running through these studies of the liver, lungs, heart, kidneys, and eyes is the lack of toxicity of methadone even when given in large doses over long periods of time.

The effects of methadone on sexual hormones and functioning are not quite as clear as the organ systems just reviewed. Dr. Kreek has described the effects of chronic methadone use on testosterone, prolactin, and other hormones. She points out the problems involved, such as the lack of control for other drugs and the inconsistency of some of the results. She failed, however, to mention one paper which is of interest because, although it did not get into laboratory values, it did show a statistical relationship between methadone dose and sexual behavior. Crowley and Simpson (1978) found that higher doses of methadone led to decreased sexual behavior, especially in female addicts. They note that although dose was not the only determinant, it accounted for 40 percent of the variance in female and 10 percent of the variance in male sexual contacts. The patients had been on methadone an average of over 30 months. The study was openended and nonblind, but the area is important enough that it should certainly be replicated in a controlled fashion and attention paid to the use of other drugs and the presence or absence of chronic liver disease.

Dr. Kreek mentions the observation of edema during early stages of methadone and attributes it to the well documented acute narcotic effect of antidiuretic hormone release. This effect, however, may not simply be an acute one, as is noted by an article by Longwell et al. (1979) describing three patients with massive edema who had been maintained on methadone for 3 to 6 months, with edema worsening rather than improving over time. In reviewing these cases, however, I noted that all of the patients were maintained on at least 100 milligrams of methadone. It may be, therefore, that tolerance to the ADH release is slower to occur or incomplete at very high doses of methadone.

The final chronic effect of methadone that I would have liked to see expanded upon by Dr. Kreek has to do with its effect on sleep patterns. She notes that about 20 percent complain of sleep problems and these are primarily the problem of insomnia. In a recent study by Orr and Stahl (1978), comparing five methadone-maintained patients to five normal controls, the methadone patients have been on methadone from 2 months to 23 months on doses ranging from 40 to 120 mg. It was found that methadone patients had a significantly decreased REM and stage 4 latencies and increased stage 1 and slow wave sleep percentages. No relation was found between these changes and either dosage or duration of time on methadone. The increase in percent of stage 1 sleep is indicative of an increased level of arousal and thus differed from the findings by Kay (1975), who found methadone to have a sedating effect. Also, Kay did not find any significant alterations in slow wave sleep. These changes in stage 1 would go along with the clinical finding of complaints of insomnia.

In conclusion, I have no quarrel with Dr. Kreek's summary that although there are many interesting physiological and biochemical alterations related to methadone use, there are minimal side effects that are clinically detectable, and toxicity during chronic treatment is very rare. Where major problems do occur, they seem to be related to either ongoing preexisting chronic diseases, to coexisting new diseases or illnesses, or especially to polydrug or alcohol abuse. Nonetheless there remain areas where research efforts should be focused and, in particular, I would opt to study further the effects of methadone in the endocrine area and on sleep.

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DISCUSSION SUMMARY

Barbara Gastel, M.D.

This discussion was relatively brief and focused first on the possible significance of the association of choreic movements and other neurological disturbances with methadone use in one patient. The remainder of the discussion addressed topics for further research.

The participants seemed to show perplexity over the report of the patient with a methadone-associated neurological disorder. They appeared to agree, however, that the case was very complex and that such a syndrome has not been noted as a complication of methadone in any other case. It appeared that the participants did not consider the subject a top priority for investigation.

Several major areas for further research were identified. The need for well controlled studies of sexual, reproductive, and endocrine function in both male and female methadone users was emphasized. Also noting that insomnia seems to be of considerable concern to patients and may contribute to recidivism, they called for research on sleep in methadone-maintained individuals. The interaction between endogenous and exogenous opioids was likewise cited as an important field of study, especially because it could yield clues to the roles of the former. In addition, participants endorsed the long-term followup of methadone users, some of whom now have been receiving the drug for 17 years.

PART III

FACTORS AFFECTING THE OUTCOME OF METHADONE TREATMENT

INTRODUCTION

Roger Meyer, M.D.

Methadone maintenance marked the formal return of physicians to the care of the opiate addict after an absence of more than half a century. Yet few physicians in these programs today play a key policy role or a direct patient care role in methadone treatment. With few exceptions, Herbert Kleber, Edward Senay, and George Woody among them, we have failed to interest and to educate a new generation of psychiatrists, internists, and public health physicians to come into this field.

Our concept of methadone treatment has evolved from the separate experiments in British Columbia and at Rockefeller University in the 1960s. The British Columbia model evolved empirically as a program of long-term detoxification designed to keep patients in an abstinence oriented outpatient program. Vincent Dole and Marie Nyswander's approach at Rockefeller University was based on a theory that the opioid addict was metabolically "different" and required methadone much as the diabetic requires exogenous insulin. The theory is still unproven, but recent research on endogenous opioids and the opiate receptor promise a future scientific examination of this hypothesis. Despite the limitations of the theory, Dole and Nyswander's major and lasting contributions were in a group of studies indicating the safety, efficacy, and acceptability of methadone treatment. They also addressed the question of eventual detoxification. In all of their work they emphasized evaluation. They set up the Gearing Committee which made the following recommendations:

1. Methadone maintenance programs should include at least the following elements in order to constitute proper medical practice:

    a. adequate facilities for the supervised collection of urine and for frequent and accurate urine testing for the presence of morphine and other drugs;

    b. general medical and psychiatric services;

    c. hospital facilities as needed;

    d. adequate staff; and

e. rigid controls of methods of dispensing methadone to prevent diversion to illicit sale or to possible intravenous use.

2. Care should be exercised in the selection of patients to prevent the possibility of causing the person who has not been dependent on heroin to become dependent on methadone.

3. There should be continued evaluation of the long-term effectiveness of methadone programs for persons who are stabilized on an inpatient or an ambulatory outpatient basis.

4. Where feasible, staff members of new methadone maintenance programs should be trained in an established effective program.

5. Continuing research is essential, particularly with reference to:

   a. the use of properly trained practicing physicians as an extension of organized methadone maintenance programs in the management of those patients whose needs for allied services are minimal. These patients should remain in contact with the methadone maintenance program for periodic evaluation, including urine testing;

   b. the role of methadone maintenance in the treatment of heroin dependent patients under 18 years of age; and

   c. the use of methadone maintenance in combination with other approaches to the treatment of morphine-type dependence.

Methadone maintenance was derided as "nothing new" by many distinguished pharmacologists. In a landmark study, William Martin studied the effects of methadone on hydromorphone (Dilaudid) self-administration in an operant paradigm. His findings were consistent with urine test results in a large number of patients in methadone clinics. In the latter setting, 20 percent of urines screened for opioids are positive on any given day. In Martin's laboratory study, two of the nine subjects continued to administer hydromorphone despite methadone treatment. Martin's formulation was behavioral rather

than metabolic. Methadone treatment has also been described as psychotherapeutic in the writings of Perkins and Block and Khantzian.

Over the past 15 years, we have crossed a number of milestones in the use of methadone treatment in addition to the above. The following developments stand out in the evolving state of the art:

1. Outpatient induction of methadone treatment rather than inpatient induction.

2. The introduction of L-alpha acetyl methadol (LAAM).

3. The Goldstein proposal of sequential steps from opioid substitution through treatment with narcotic antagonists to an eventual drug free state.

4. Changes in the dosage from high doses of 80 to 100 mg/day to about 50 mg, and recent controversy about the efficacy of lower doses.

5. A number of approaches to detoxification, including Senay's classic study of methadone detoxification, and the work of Kleber and his colleagues utilizing clonidine for detoxification, and of Richard Resnick utilizing rapid detoxification with naltrexone.

6. The use of the data from the Drug Abuse Reporting Program to define the patient and treatment characteristics associated with differential treatment outcome.

We are at an interesting crossroads. In recent years it has been said that things begin in California. Certainly, the enthusiasm for cutting back support for social programs came on the national scene with the passage of Proposition 13 in California. A recent paper by Dr. William McGlothlin describes the impact of such budget cuts on the closing of a methadone clinic in Bakersfield, California. With the introduction of block grants, the significant role played by the Federal Government in developing drug abuse treatment programs on a nationwide basis will be significantly reduced. There will be fewer funds and there will be fewer directions from Washington on the essential elements within a service program. The issue will be decided on a state-by-state basis.

Perhaps this book provides an optimal occasion to define what we have learned over the last 15 years of methadone treatment and what we have learned of the optional program package. I think that we would all agree that methadone maintenance reduces the frequency of illicit opiate use among heroin addicts. In general, it leads to a decrease in illegal activity and will generally increase employment rates among employable individuals. There remain many lingering questions regarding the possibility of eventual detoxification from methadone maintenance. It is possible that some people may require lifetime methadone administration--or at least methadone administration for many years. We do not know how to differentiate those patients who could be detoxified from those patients who may require long-term maintenance. Moreover, over the last few years we have seen an increase in the dropout rate during the first year of treatment. The dropout rate has gone from 15 to 35 percent. Are we able to identify the characteristics of patients who are at high risk of dropping out and can we provide a treatment package that will make retention in treatment more likely?

In the early days of the Special Action Office for Drug Abuse Prevention (SAODAP), the Federal Government identified a per capita cost--reimbursement for patients in methadone treatment. Programs were given some flexibility in how reimbursements were allocated. It is not yet clear that we can identify an optimal staffing pattern within methadone clinics. The data on psychotherapy, which is reviewed in subsequent papers, suggest that psychotherapy can be useful where patients avail themselves of this treatment, but many patients reject what is offered. Advice on staff training and experience and of admissions and discharge procedures might be offered to the States as they take over more of the functions of regulating methadone treatment. What can be said of an optimal methadone take-home policy? Finally, are we returning again to the question of dosage and are there new data to suggest that 50 mg of methadone per day is inadequate?

For NIDA the question must be what its role can and should be in defining the future of methadone treatment. NIDA has established a model evaluation program which has been used to assess treatment efficacy. Can this program be maintained to provide timely information on changes in patient characteristics and treatment strategies? The

information within Part III suggests a number of directions for policy studies and for basic and clinical research. In all of these areas, it is clear that NIDA has the preeminent responsibility for funding.

In retrospect, we are at a mature stage in viewing methadone treatment. It is clear that methadone maintenance is not a cure-all for all addicts. The failures need to be understood on the basis of the complexity of the "black box," the characteristics of the patients and of therapist/counselors, and of the mix. What are the optimal variables to examine in this pursuit as we move beyond the present state of the art? The information within Part III suggests some strong leads which we should be able to expand upon in our discussions.

CHAPTER 1. PATIENT CHARACTERISTICS ASSOCIATED WITH OUTCOME

A. Thomas McLellan, Ph.D.

INTRODUCTION

The early reports of Dole, Nyswander, Cushman, and others (1966; 1972; 1965) established the safety and pharmacological efficacy of methadone in the treatment of opiate dependence. Since that time, the clinical efficacy of methadone maintenance has been evaluated in over 275 published reports (Bale et al. 1977; Brecher 1972; Burt et al. 1980; Charuvastra et al. 1980; Gearing 1971; Gearing and Schweitzer 1974; Sells 1974; Sells and Simpson 1976). While there has been considerable variability in the methodology and results of these studies, the weight of evidence clearly indicates that the majority of opiate dependent patients show significant improvements in opiate and nonopiate drug use, employment, and illegal activity during methadone maintenance treatment (Gearing 1971; Sells 1978).

This information appears to substantiate and legitimize the role of methadone maintenance as a therapeutic modality in the treatment of opiate dependence. It therefore becomes reasonable to ask why so much time and effort continues to be directed at predicting outcome from methadone treatment. In fact, outcome prediction studies are particularly long and expensive endeavors which historically have not produced robust or generalizable conclusions (Klein 1977; Luborsky and McLellan 1978; Szapocznik and Ladner 1977). Yet in the case of methadone maintenance, there are three reasons why careful, well designed, predictive studies may be considered essential. First, if we accept as fact that methadone maintenance is effective, we still do not have specific information on why it is effective or how it promotes improvement. Secondly, there are practical risks and costs associated with methadone treatment that reduce its suitability for the entire patient population. Methadone is of course addicting, leaving patients subject to associated problems of addiction and leaving society responsible for maintaining patients and for safeguarding the integrity of the treatment effort against misuse. Finally and perhaps most importantly, the very nature of methadone maintenance treatment is ideologically controversial, even within the field of drug abuse

treatment (Brecher 1972; Epstein 1974; Maddux and Bowden 1972). While most workers recognize and accept the use of methadone on a short-term basis to withdraw a dependent patient, the maintenance of these patients on a synthetic opiate over long periods of time is considered by many within the field to be indicative of rehabilitation failure (Brecher 1972; Cole and Watterson 1976).

In light of these factors, "general conclusions" regarding the "overall effectiveness" of methadone in the "majority of patients" are not adequate. The decision on whether or not to treat a potential candidate for methadone requires that the results of methadone maintenance be examined in detail as a means toward identifying the particular patient and program characteristics which are most related to treatment response. As a means toward advancing scientific response to these issues, this paper will review and discuss existing evidence linking patient factors with response to methadone maintenance treatment of opiate addiction. The paper is presented in five sections. The first section raises several basic ideological, conceptual, and methodological issues associated with the treatment goals of methadone maintenance and with the scientific basis of outcome prediction. The second section presents a descriptive summary of studies which have related patient demographic, background, and performance characteristics to retention in and response during methadone maintenance. Section three examines the same patient factors in relation to response following methadone maintenance. The fourth part builds upon the general findings from parts two and three to examine those patient characteristics that are differentially predictive of response to methadone maintenance, that is, those characteristics which predict better response to methadone maintenance than to other treatment alternatives such as drug free outpatient treatment or inpatient therapeutic community. The final section of the paper summarizes, discusses, and criticizes the existing data and presents some personal conclusions regarding the need for future studies.

SECTION I--CONCEPTUAL AND METHODOLOGICAL CONSIDERATIONS

Prediction of outcome from methadone or any other form of treatment is a complex process requiring conceptual clarity regarding the types of outcome expected and methodological sophistication regarding the design, conduct, and analyses of the studies. As a preface to the review of

the literature it is necessary to delineate the conceptual and methodological factors which have influenced the data to be presented.

Conceptual Factors

There are clear and important conceptual or ideological differences among workers in the field with regard to the appropriate role of methadone in an overall treatment plan. These conceptual differences have led to different treatment strategies with separate and distinct definitions of favorable outcome.

Methadone as a maintenance drug. Methadone has been offered to patients as a long-term maintenance modality under the overt or implicit assumption that methadone can supply a biological or psychological "element" which is lacking in addicts (Brecher 1972; Cole and Watterson 1976; Dole and Nyswander 1965, 1966; Dole et al. 1976). The goal of treatment under this conceptual framework is to stabilize the patient on a comfortable dose of methadone, and then to retain him in treatment to provide ancillary services such as medical care, psychotherapy, job training, and legal counsel. As the patient becomes socially, psychologically, and medically stable he may be gradually weaned off methadone, but withdrawal is generally not seen as a necessary or appropriate goal for all patients.

Methadone as a temporary substitute. Many, if not most workers in the field of drug abuse treatment consider drug free living to be a realistic and important goal for the majority of opiate dependent patients. Under this conceptual approach low doses of methadone are used and for relatively short periods of time with sustained attention toward the goal of withdrawal. Ancillary services and treatments are provided but generally the focus of rehabilitation remains upon the drug problem, under the assumption that this problem is central to the overall rehabilitation of the patient.

These ideological and therapeutic differences within the treatment community about the methadone maintenance modality have been discussed in detail by Cole and Watterson (1976). Clearly these differences are important to an evaluation of treatment effectiveness and to the prediction of outcome. The discrepancy in treatment goals has been reflected in the published studies and is addressed in the subsequent review. The first part of section II

deals with those patient characteristics which have been related to retention in, and performance during, methadone maintenance. The second part of section II discusses patient factors associated with good performance following methadone maintenance.

Methodological Factors

Prediction of treatment outcome requires more methodological sophistication than any other aspect of data analysis. This and the multiple design limitations in clinical research, have resulted in predictive studies being the most confounded, misinterpreted, and unreliable within the field. In the course of reviewing the published literature on prediction of methadone outcome, several methodological problems were seen, and they are discussed briefly as a means of sharing the review strategy employed.

Data collection. Ideally, all patient data should be collected by technicians who are independent of the treatment process. The outcome data should be collected at fixed points during or following treatment and several measures of outcome should be provided besides drug use. The majority of clinical research studies have not met all of these criteria. In this review no studies were rejected unless they had major violations on most of these criteria. However, it is important to note that different predictors may apply for different outcome variables (e.g., drug use, employment, legal status) (McLellan et al. 1981b; Simpson et al. 1978) and that performance on one measure of outcome (e.g., drug use) is not necessarily correlated with performance on other measures of outcome (McLellan et al. 1981).

Prospective vs retrospective analyses. Greater consideration and emphasis has been given to studies which have tested specific predictors that were to be related to outcome based upon prior work or a relevant theory. Results from these prospective studies hold greater conceptual validity than those derived from a large-scale retrospective analyses of a collection of potential predictors (Cohen and Cohen 1975; Gottheil et al. 1981; Klein 1977). It should be clear that retrospective analyses, especially those in which a large number of items are examined, run the risk of simply uncovering an isolated or spurious relationship. Simple correlations between sets of predictors and an outcome variable do not provide important information regarding the relationships among the predictor

variables. This information may be central to an interpretation of the truly effective predictors of treatment outcome. In the present review, retrospective studies were included if their methods were adequate and if the results were justifiable on conceptual or clinical grounds.

Differentiation or prediction. Perhaps the most common misinterpretation of results occurred in retrospective studies where poor performance patients (based on some valid criterion) were found to be significantly different from good performance patients on variable X. Results such as these were often extrapolated to the conclusion that patients with variable X should not be treated in methadone maintenance. Depending upon the variability in the population and the number of subjects utilized, it is possible for many variables to be "significantly different" among segments of the population. However, these variables may not be meaningfully associated with the outcome measure in a predictive sense. This may happen because variable X accounts for only a very small part of the total variation in the outcome measure or because X is closely related to another variable (which may or may not have been included) that is itself predictive of outcome (for a review, see Gottheil et al. 1981; Simpson et al. 1978). Reliable and valid estimates of predictability require multivariate analyses which can take into consideration these complex relationships and adjust the estimates of prediction appropriately. Existing studies were evaluated individually for methodological rigor and consistency. Only those which were clearly misinterpreted or confounded were excluded.

A total of 113 studies involving prediction of outcome or differentiation of good and poor performance in methadone maintenance were reviewed. Thirty-seven of these studies were considered too weak or too poorly conducted to permit a useful interpretation. Seventy-six studies have been included in the subsequent analysis. It should be noted that throughout the review of predictive studies, the work of Simpson, Sells, Demaree, Hornick, Joe and the other members of the TCU-DARP program stands out as being conceptually and methodologically superior to almost all other work. Much of the final commentary is based upon their findings (Sells 1978; Sells 1974; Sells et al. 1980; Sells and Simpson 1976; Sells and Simpson 1980; Simpson and Joe 1977; Simpson et al. 1976; Simpson and Savage 1976; Simpson et al. 1978).

SECTION II--PREDICTORS OF RETENTION AND PERFORMANCE DURING METHADONE MAINTENANCE

Retention has been viewed as an important goal of methadone treatment in its own right, under the assumption that it is a preferable alternative to the use of street drugs and that it provides a vehicle for the delivery of important ancillary services (Szapocznik and Ladner 1977). It is also important from the perspective of evaluating post-methadone outcome since during-methadone performance has been reliably associated with post-methadone status (Lofchie et al. 1974). A review of the 113 studies indicates that approximately 15 to 35 percent of patients drop out of methadone maintenance prior to 12 months (Babst et al. 1971; Babst et al. 1976; Boudouris 1976; Gottheil et al. 1981; Klassen 1977; Kotzker et al. 1979; Krakowski and Smart 1974; MacFarlain et al. 1977; NAPAD 1973; Szapocznik and Ladner 1977; Williams and Johnston 1972), which has generally been a desirable treatment duration (Szapocznik and Ladner 1977). Thus, the studies to be reported in this section have used patient demographic and background factors to differentiate the 15 to 35 percent of patients who drop out of treatment from those who do not.

Demographic Factors

Age. Age has been studied as a predictor of treatment retention in 31 of the studies. Eight studies have shown no relationship and two have found that younger patients stay longer, but the large majority of studies have found that older patients are more reliably retained and have better during treatment performance. Babst et al.(1971) performed a retrospective analysis of 24 variables in an attempt to discriminate the 20 percent of patients in their program who left methadone maintenance prior to 1 year. Patients younger than 25 were significantly more likely to have left treatment than older patients. Similar findings have been reported by most authors, and some of the most representative include Szapocznik and Ladner (1977), Williams and Johnston (1972), and Neman et al. (1977). An estimate of the strength of prediction based upon the collective reports suggests that age may account for approximately 8 to 10 percent of outcome variance across all studies depending upon the population and the outcome measures.

Race. Race has not been as widely studied as age, and the results are not quite as consistent. However, seven studies did report that black or nonwhite patients were retained longer than white patients. Sechrest and Crim (1979), for example, found that black patients stayed in treatment longer and had more pronounced reductions in criminal behavior during methadone maintenance. If race is a significant predictor of treatment retention, the available data indicate that it accounts for no more than 5 to 8 percent of outcome variance.

Sex and education. Sex and education have not shown evidence of being significantly related to methadone treatment retention. In the case of sex, only six studies surveyed had a significant proportion of women, and none of these studied sex as a predictor (Rosenthall et al. 1979). Education was widely studied but showed virtually no correlation with retention in or adjustment during treatment (Babst et al. 1971; Lofchie et al. 1974; Sechrest and Crim 1979; Williams and Johnston 1972).

Marital status. This factor was studied in 12 reports, and all found that marriage or a stable relationship was significantly and often profoundly related to duration of treatment. The review by Szapocznik and Ladner (1977) reported five studies in which married patients were significantly more likely to remain in methadone maintenance than nonmarried patients. The published correlations between marital status and treatment retention are quite variable, due in part to methods of calculating the correlations (point-biserial, tetrachloric), yet the data suggest that this variable may account for at least 8 percent and as much as 18 percent of variance in treatment duration (Babst et al. 1971; Boudouris 1976; Klassen 1977; Krakowski and Smart 1974; NAPAD 1973; Stanton 1979; Szapocznik and Ladner 1977).

Thus, age, marital status, and possibly race are the demographic variables which are most associated with retention in methadone treatment. It is not possible to judge the amount of shared variance associated with these variables, but it appears reasonable to conclude from the published correlations, that they could jointly account for 10 to 20 percent total variance in retention.

Background and Patient History Factors

Employment and work history. Thirty-one studies of retention examined employment history as a predictive factor in methadone maintenance. Twenty-six of these studies reported significant, positive correlations between employment status at treatment admission and methadone retention/performance. McLellan et al. (1981a) examined the performance of methadone maintenance patients who were divided on the basis of the source of the majority (40 percent or more) of their pretreatment income, into employment (N=16), welfare (N=23), or illegal income (N=18) groups. Analyses of 21 performance criteria, covering a wide range of adjustment areas, indicated that both the employment and illegal income patients showed considerable improvement in drug use, employment, and illegal activity. However, the welfare group showed no significant improvements in any of the 21 criteria despite equal or greater lengths of treatment. A study by Gearing and Schweitzer (1974) reported a retrospective examination of factors associated with retention in methadone maintenance in 17,500 patients. These authors found 90 percent retained after 1 year and steady increases in social productivity (employment, in school, homemaker) throughout treatment. Skilled or semi-skilled patients showed the greatest retention, as well as the most improvement in drug use and employment. Similar conclusions were reported by Babst et al. (1971) in a retrospective study of 138 patients admitted to methadone maintenance. Retention was not related to nine other demographic and patient background variables, suggesting the possibility that the relationship was spurious in this case. The majority of published studies have found employment or work history to be a major factor associated with treatment retention. The published correlations suggest that this variable may account for 8 to 12 percent of variability in duration of treatment retention (Babst et al. 1971; Krakowski and Smart 1974).

Criminal history and illegal activity. Criminal history and illegal activity have been widely studied both as a predictor of patient outcome and as performance criteria due to a link with drug use and to society's concern with criminal behavior. Unfortunately the published work using criminality as a predictor has suffered greatly from situational and methodological constraints. The weight of evidence (virtually all retrospective) from 46 studies

indicates that a more extensive criminal background is associated with less time in treatment and poorer performance during treatment in most methadone maintenance programs (Babst et al. 1971; Babst et al. 1976; Kotzker et al. 1979; Krakowski and Smart 1974; McFarlain et al. 1977; Szapocznik and Ladner 1977). One study which has investigated this factor bears further reporting. Sells and his colleagues from TCU examined factors which predicted favorable response during methadone treatment in 821 subjects interviewed by independent technicians (Sells et al. 1980; Sells and Simpson 1980; Simpson et al. 1978). They investigated several during-treatment criteria including drug use, employment, alcohol use, and social deviance (adherence to program regulations), and criminal background was the major performance predictor on all but the alcohol use criterion (Simpson et al. 1978). Greater criminal history was associated with poorer during-treatment performance but only accounted for an average of 7 percent of the outcome variance across outcome measures.

Severity and type of drug use. Severity and type of drug use has also been extensively studied as a predictor of retention. Of 27 studies that reported a correlation between the severity of opiate addiction (measured as either the amount of opiates used, the length of addiction, or both), only two studies indicated that this was significantly related to performance (Klassen 1977). The data therefore suggest that the severity of opiate use is at best poorly related, if not unrelated, to performance during methadone maintenance. However, 17 studies did report a significant relationship between the use of multiple drugs at admission (including alcohol) and poor retention or poor during-treatment adjustment (Barr 1978; Barr et al. 1977; Babst et al. 1971, 1976; Bihari 1974; Boudouris 1976; Lofchie et al. 1974; Szapocznik and Ladner 1977). Williams and Johnston (1972) performed a retrospective analysis of 23 factors in an attempt to differentiate the sample of 185 methadone patients who left prior to 1 year from the 155 who remained in treatment. They found that those who stayed in treatment had an average of 12 years of heroin use versus 5.5 years in the early termination group, and the early terminators had more than twice the proportion of multiple drug users. The study was performed retrospectively in a post hoc exploratory manner without the use of multivariate analyses, yet the size of the sample and the nature of the relationships reported does suggest that this characteristic may be a significant predictor. The data from this and other reports do not

permit a reasonable estimate of the strength of the relationship.

Psychological factors. Factors such as personality profile and symptoms of major psychiatric disorders have also been related to methadone maintenance retention. The majority of these studies have been prospective attempts or well defined retrospective tests of specific hypotheses (Craig 1979). Thus, many of these studies offer greater conceptual or methodological rigor than most other predictive analyses. It has been somewhat surprising that after examining 33 published reports using these variables as predictors, there are virtually no clear trends. Several studies examined the role of personality (MMPI, 16PF, and others) (Craig 1979; Krakowski and Smart 1974; McFarlain et al. 1977; Ottomanelli 1977). Results have been extremely variable and no study has demonstrated a meaningful relationship between personality profile and during-treatment response (Craig 1979). A few studies have shown significant relationships between measures of the severity of psychiatric symptoms or of general psychopathology and during treatment response. Pittel et al. (1972) used MMPI profiles to differentiate those patients who remained in methadone 18 months from those who left earlier. In three different replications of this study, these authors found little predictive value in the personality profiles but significant differentiation using a combination of scale scores which was most indicative of general psychopathology. Those clients with greater amounts of general psychopathology were more likely to dropout early than those who were less impaired. In a similar study, Levine et al. (1972) found a combination of symptoms such as anxiety, depression, and thought disorder was the best predictor of early dropout from methadone maintenance. Similar results have been reported by McLellan et al. (1983a) using a simple 10-point interviewer rating of the severity of the patients' overall psychological problem as a predictor. These authors found that this general estimate of psychopathology was the single best predictor of overall response to methadone maintenance or to therapeutic community treatment. They report that this variable accounted for an average of 10 percent outcome variance across seven criteria in 282 subjects. This particular study is discussed in more detail in section III. While many studies have examined descriptive aspects of psychopathology, such as diagnosis and personality profiles, these have failed to show any consistent results. Those studies which have used quantitative measures of symptom severity or psychopathology show

promise but are not sufficiently developed to permit a reasonable estimate of their potential contribution to outcome prediction.

The available data suggest that criminal background, poor work history, use of nonopiate drugs, and possibly greater severity of psychological problems are the major patient background variables which are predictive of poor retention in and performance during methadone. It is interesting that education, personality measures, psychiatric diagnosis, and especially the duration of intensity of opiate use have not shown evidence of significant predictive value. It is not possible from the available data to determine which of the demographic and patient background variables are interrelated, or which are the most powerful predictors. However, the data do suggest that the best combination of demographic and patient background variables probably account for 25 to 45 percent of variation in treatment retention or during treatment performances.

SECTION III--PREDICTORS OF PERFORMANCE FOLLOWING METHADONE MAINTENANCE

While more than 100 studies have reported on the postwithdrawal status of drug abuse patients, only those that result from a prior period of methadone maintenance will be discussed here. No studies of withdrawal from street drugs or of withdrawal as the primary treatment modality are reviewed. A major question is whether the same variables which predicted retention and performance during methadone maintenance will predict performance following methadone maintenance. Based upon the proportion of patients who actually accomplish sustained drug free status after methadone maintenance, it appears that prediction of successful withdrawal may be quite different from prediction of successful adjustment during methadone maintenance. There is an extremely small percentage of potentially eligible patients who actually complete withdrawal from methadone maintenance, and this has been summarized effectively by Cushman (1974) in a study of 396 patients admitted to the Saint Lukes Hospital Methadone Maintenance program. Two hundred forty of the 396 patients actually became active or engaged in treatment. One hundred ninety-six remained in treatment for 6 months and were considered potentially suitable for withdrawal, but only 168 were eligible based upon stable performance. One hundred eighteen of these patients attempted withdrawal, but only 54 patients achieved a drug free state (defined as 2

days at zero dose), and only 40 of these were "functioning well" at 1-month follow-up. Thus, only 13 percent of admitted patients were able to complete a withdrawal, which illustrates several of the methodological problems inherent in predictive studies. If, for example, we were interested in the factors which differentiated those 54 patients who completed withdrawal from the 118 who were eligible and attempted it, we could find several potentially significant factors. However, these significant factors may be much different from the characteristics which differentiate the 54 who achieved a drug free state from the 396 patients admitted to treatment. This issue will be discussed in greater detail in section IV.

Because of the low proportion of patients who actually complete a sustained withdrawal from methadone maintenance and because of the many methodological problems associated with attempts to classify those who completed, or to account for their posttreatment performance, only 19 studies were included in this review. Very few of these studies could be compared across types of variables used as predictors or on the outcome measures. The conclusions expressed here reflect a consensus based upon general findings from the pertinent studies rather than a critical examination of the types of variables and their specific contributions to prediction of outcome.

Demographic Factors

Factors such as age, race, sex, and education have been variously studied in association with completion of withdrawal and posttreatment functioning in virtually all of the 19 studies considered. No significant relationships were shown (or claimed by the authors) with regard to race, sex, or education level (Burt et al. 1980; Charuvastra et al. 1980; Neman et al. 1977; Riordan et al. 1976; Stimmel et al. 1978; Stimmel et al. 1977). Age was significantly associated with a greater likelihood of completing withdrawal in a study by Panepinto et al. (1977). These authors reported that younger patients were more likely to complete withdrawal but the results are not easily compared with those of most other studies since the population was predominantly female, with fewer years of addiction. In addition, age here was probably confounded by years of addiction so that the significant association may reflect a joint effect. Three other studies reported that older patients with more years of addiction were more likely to complete withdrawal and/or to remain drug free

following treatment. It is not possible to resolve this discrepancy from the reported data. It may be that young, recently addicted patients and older patients who have reached a point of maturation in their drug use careers are more successful following withdrawal than the remaining population, but this remains conjecture. Regardless of the nature of the association between age and post-methadone performance, the data suggest that it is not a major factor in predicting outcome.

Background and Patient History Factors

Three studies have investigated patient background and history variables as a means of predicting successful withdrawal from methadone maintenance. A study by Riordan et al. (1976) attempted to differentiate patients who were drug free from those who used drugs following methadone maintenance in a sample of 38 males who completed withdrawal. While this study did collect urinalysis results to validate their outcome measures, there were 26 who fell into the nonuse category and 12 who continued to use drugs. Despite this small sample, the study found that patients with shorter addiction history, less multiple drug use, and lower socioeconomic status were more likely to be drug free following withdrawal. The authors found that legal pressure but not a history of employment was also related to posttreatment success.

Stimmel et al. (1978) used a multiple discriminant analysis to classify patients who were not using opiates from those who were, following withdrawal from methadone maintenance. The follow-up interval was variable across patients from 6 months to 5 years, though the average period of follow-up was approximately 26 months. The analysis indicated that a stable family situation, employment history, and fewer years of opiate use at the time of admission were among the best variables differentiating the two groups. It should be noted that while the combination of variables did correctly identify 71 percent of the subjects, this was only slightly better than chance prediction, since 65 percent were in the drug-using group.

Cushman (1974) has also attempted to differentiate those patients (N=40) who showed stable, successful functioning 1 month after withdrawal from the 118 who attempted withdrawal. His results suggested that patients who were more

"socially assimilated" (e.g., employed, living with family) were more likely to show stable functioning at 1 month after withdrawal.

Each of these studies has methodological problems significant enough to warrant caution in the acceptance of the conclusion, yet all studies have come to essentially the same conclusion, and these are generally consistent with clinical experience. The data suggest the importance of patient background and history (especially socioeconomic status and work history) as direct predictors of post-treatment function. However, it is not possible from these studies alone to determine the extent or importance of these relationships in comparison with other factors.

During-Treatment Performance

Length of treatment has been studied in seven reports as it relates to posttreatment performance (Bale et al. 1977; Boudouris 1976; Burt et al. 1980; Lofchie et al. 1974; Panepinto et al. 1977; Riordan et al. 1976; Stimmel et al. 1977). In all but one study (Panepinto et al. 1977), the length of time on methadone was positively related to the likelihood of withdrawal success and to posttreatment measures of drug use, employment, and crime. Dosage level immediately before detoxification has also been related to posttreatment outcome in nine studies, and all have concluded that patients who were able to be maintained on lower dosages showed greater withdrawal success and generally better posttreatment performance (Riordan et al. 1976; Stimmel et al. 1978). In most studies, time in treatment and dosage level have been among the major predictors of success, and the data suggest that these factors may account for 15 to 25 percent of outcome variance.

However, these predictors are more self-serving than informative since it is almost always necessary for a patient to stabilize on a low dose prior to withdrawal, and it is usually necessary for patients to adjust to lower doses gradually over time. Thus, the real question in this issue is, what factors predict the ability to stabilize on low dosage?

In summary, the data on successful withdrawal and adjustment following methadone maintenance suggest that only a small proportion (10-20 percent) of admitted patients are able to accomplish this goal (Sells 1978; Stimmel et al. 1978). The factors which appear to be the most promising

predictors of successful outcome include employment, stable family relations, the ability to stabilize on low dosages of methadone immediately before detoxification, and possibly age (although the direction of this latter relationship is unclear). Considering the amount of variation present in this outcome measure, even the best combination of these variables cannot account for very much. Thus, the predictability of this outcome measure, and perhaps its therapeutic advisability, remain questionable at this writing.

SECTION IV--DIFFERENTIAL PREDICTION

Thus far, this paper has presented data from studies which have examined the patient factors associated with retention in methadone maintenance and with favorable performance following methadone treatment. In general, data from these diverse studies have shown that older patients with less multiple drug use, greater work skills, more stable home lives, and less psychopathology at treatment admission, show the best performance. These data are hardly surprising. Conclusions such as these have been reported by workers in other fields as diverse from methadone maintenance as psychotherapy (Luborsky 1980). In short, those patients with the greatest assets and least serious problems will profit most from virtually any intervention. Obviously, these data are less than satisfactory with regard to understanding the specific strengths of methadone maintenance treatment or its optimum patient matches.

However, two groups of investigators have attempted to examine those patient factors which would differentially predict better outcome in methadone maintenance than an alternative treatment such as therapeutic community (TC) or drug free outpatient treatment (DFOP).

Sells, Simpson, Demaree, Hornick, Neman and the other members of the Texas Christian University (TCU) staff have compiled intake, during treatment, and 1-year follow-up data on patients from 52 drug abuse treatment programs across the country since 1969. The admission and during-treatment data have been collected by members of the treatment programs' staffs and the follow-up data were collected by the National Opinion Research Corporation. These authors have therefore had the opportunity to examine not only the factors within each type of treatment modality which have been predictive of outcome, but also

those factors which suggest that one type of modality might be superior to another. These authors have also used the most advanced and appropriate multivariate methods to analyze their data, consistently cross-checking their conclusions with different analyses on the same cohort of patients, or with the same analyses on a separate patient cohort. This careful data collection, analytic sophistication, and generally conservative demeanor make their reports prominent in any interpretation of methadone treatment effects.

The work of the TCU group and others (McLellan et al. 1981) has indicated that different outcome measures are generally poorly related and that pretreatment factors predict these outcome measures differently (Simpson et al. 1978). In this regard, the TCU workers have examined outcome profiles on six posttreatment measures (employment, opiate use, nonopiate use, alcohol use, crime, and treatment) (Hornick et al. 1977; Neman et al. 1977; Simpson and Joe 1977).

Table 1 summarizes the findings of the TCU group regarding factors which significantly predicted poor outcome on five criteria in three different treatment modalities. Detoxification in this case refers to withdrawal directly from street drugs instead of withdrawal following sustained methadone maintenance. As can be seen, there were significant differences in the nature of the predictors among these three treatment options. Only pretreatment criminality was a significant predictor of poorer outcome for detoxification. This was due in part to the more uniformly poor outcomes associated with this modality and in part to the simple inability of prediction. Greater criminal background and poorer employment histories were significant predictors of poor outcome on several post-treatment criteria for methadone maintenance, but they were generally unrelated to performance in therapeutic communities. Another interesting difference among the programs was that younger patients did significantly worse than others on most criteria in methadone maintenance, but this was not a factor in therapeutic communities. Finally, shorter treatment duration was significantly associated with poorer outcome for both groups but predominantly so for therapeutic community patients.

In summary then, the younger drug abusing patients who had high levels of criminal background and poor employment histories were particularly poorly suited to methadone

Table 1. Factors predicting poor 1-year outcome on five criteria from the TCU-DARP study

Criterion	Methadone Maintenance	Therapeutic Community	Detoxification
Opiate use	Younger at admission Higher criminality Higher addiction Shorter treatment	Poor during-treatment performance Shorter treatment time	Higher criminality
Nonopiate use	Higher criminality Poor during-treatment performance	Higher nonopiate use Shorter time in treatment	---- ----
Employment	Lower employment Good during-treatment performance	Higher social responsibility Longer time in treatment	----
Any jail	Younger age at admission Higher criminality Lower employment Poor discharge	Higher criminality Shorter time in treatment	Higher criminality
Composite	Younger age Higher criminality Lower employment Poor during-treatment performance Shorter treatment	Poor during-treatment performance Shorter time in treatment Poor discharge	Higher criminality

maintenance, but these factors were less related to outcome in therapeutic communities, according to the findings of the TCU studies. It is significant to note that the amount or duration of drug use was rarely a significant predictor of outcome for either modality.

The Veterans Administration (VA) study of differential outcome predictors in drug abuse treatment studied 282 patients admitted to either methadone maintenance or therapeutic communities (McLellan et al. 1980b, 1983a). In particular, this multifactorial regression design has attempted to determine the particular patient characteristics which optimally associated with favorable outcome in each of the treatment modalities. Like the TCU group, McLellan and his associates have used several measures of outcome (measured 6 months following treatment admission) and have found them to be largely independent. In their reports, independent variables were considered significant predictors only if they reached $p<.01$ levels of significance on three or more of the seven outcome measures (McLellan et al. 1983a). Although this population was somewhat older than the TCU population, and all male, several characteristics which were predictive in the TCU study were also seen in this sample.

One particular factor which was not studied in the TCU report that had the greatest impact on differential prediction in the VA study was the severity of patients' pretreatment psychological problems. This was measured by a 10-point rating of severity and was judged by the admission counselor from reports of recent and past symptoms of anxiety, depression, suicidal thoughts, thought disorder, paranoia, confusion, and inability to control violent behavior (McLellan et al. 1979, 1980a). It is important to note that this measure was not based upon symptoms of drug use, criminality, or family relations, which were assessed separately. A body of data now indicates that these severity estimates can be rated reliably and are well related to other standardized measures of symptom severity (e.g., Maudsley Neuroticism Scale, Beck Depression Inventory, Hopkins Symptom Checklist) (McLellan et al. 1979, 1980a).

The predictive data, based upon multiple regression analyses and multiple analyses of covariance on seven 6-month outcome criteria (drug use, alcohol use, employment, medical condition, legal status, family relations, and psychological status) indicated that psychological severity was

the best overall predictor of improvements and posttreatment outcome in virtually all criteria and for both methadone maintenance and therapeutic community programs, accounting for an average of 10 to 12 percent of outcome variance. Further, when the total population was divided into low, medium, and high severity based on this scale, interesting outcome results emerged. For both the low and the high severity groups (approximately 40 percent of the total sample) there were very few patient demographic or background characteristics which predicted differential outcome in either the methadone maintenance or therapeutic community matching in either group, but for very different reasons. The outcome data showed that the low severity patients had generally the best improvements and the best outcome status in most criteria regardless of which modality they were treated in. The high severity patients showed some improvements but generally the poorest 6-month outcomes on virtually all criteria. In contrast, these patients did not show enhanced effects of treatment regardless of where they were treated (LaPorte et al. 1981; McLellan et al. 1983a).

Once these two groups were separated, the data for the mid-severity group did show significant factors which differentially predicted particular benefit from methadone maintenance over therapeutic community. The differential predictors for the methadone maintenance groups were older age and lower severity of employment and family problems at admission. Unlike the TCU data, criminal background was not a significant predictor of outcome, perhaps because of the generally higher level of criminal involvement throughout this population. Despite this difference, the two studies agreed that race (black) and time in treatment (longer) were among the better predictors of favorable outcome for both treatment modalities, and that age (older) and pretreatment employment history were significant differential predictors of better outcome in methadone treatment than therapeutic community.

In a follow-up study, the VA group has examined the question of what to do with those patients who show the worst response to treatment in both methadone maintenance and therapeutic communities: the patient with severe psychopathology at admission. The data indicate that these psychologically more impaired drug abuse patients show less improvement and poorer 6-month outcomes than the remainder of the patient population in either treatment modality (LaPorte et al. 1981). Further, these patients tend to be multiple substance abusers (Laporte et al. 1981; McLellan

et al. 1981b). Thus, in a recent study of psychologically more impaired patients who abused either opiates only, opiates and sedative hypnotics (e.g., barbiturates or benzodiazepines), or opiates and stimulants (e.g., amphetamines, cocaine, methylphenidate), McLellan et al. (1983b) examined whether therapeutic community or methadone maintenance showed the best outcome. Although the study was not an experimental design, the patients were selected under the condition that they could have been treated in methadone maintenance or the therapeutic community. That is, all patients met current FDA guidelines for admission to methadone maintenance, subjects were from each drug use group and were matched for number of prior treatments and for history of drug use. The results indicated that the methadone maintenance program showed significantly better outcome with the opiate-stimulant abusers, significantly worse outcome with the opiate-depressant abusers, and no difference with the opiate-only group. The authors hypothesized that methadone may act to reduce the mania and paranoia produced by the stimulant drugs, and that the regulatory and weak antipsychotic effects of methadone may be particularly beneficial to the opiate stimulant users. On the other hand, methadone and the sedative hypnotic drugs produce synergistic effects which may make it difficult for the opiate-sedative user to reduce his drug use and to concentrate upon other aspects of his rehabilitation.

SECTION V--SUMMARY AND DISCUSSION

This paper has reviewed the findings of 113 studies which have attempted to predict retention in methadone treatment, performance during methadone treatment, or successful adjustment following methadone maintenance. It should first be noted that the large majority of these studies were considered methodologically weak, often to the point of misinterpretation. We shall return to this point later.

Retention in and performance during methadone maintenance have been considered worthwhile goals for two reasons. First, many workers in the field believe that long-term maintenance is perhaps the only viable treatment goal for many patients. Secondly, virtually all workers in the field feel that successful stabilization on methadone maintenance is a necessary prerequisite to withdrawal and drug free living. The available evidence suggests that older (over 25), black, married patients show the greatest

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likelihood of 1-year treatment retention. Of these demographic criteria only age appears to be a reliable predictor over a variety of programs, and our estimate (based upon the published correlations) suggests that age plus the other demographic factors accounts for less than 25 percent of variance in length of stay criteria.

With regard to patient background factors at admission, a history of criminality, greater severity of psychological problems, and poorer employment and family status were significantly associated with shorter treatment retention. These patient history variables may be the best general predictors of early dropout and poor adjustment during methadone maintenance. The available data suggest that these patient history factors may jointly account for as much as 25 to 30 percent of variance in the length of stay criterion. It is important to emphasize that these estimates of predictive power are merely approximations based usually upon first order correlations from several different studies. These estimates may not be considered confident and may vary as much as 15 percent from study to study. Further, it is not possible on the basis of the available data to determine which of the demographic and treatment variables are interrelated, whether specific demographic variables are more predictive than certain patient history variables, or the extent to which greater amounts of treatment can override negative demographic or patient history factors. However, the review of data presently available did suggest that age (older), criminal background, employment history, psychological problems, and possibly race (black) were the major variables associated with retention and adjustment in methadone maintenance.

The goal of withdrawal from methadone maintenance and stable posttreatment adjustment has also received considerable attention through attempts to predict those patients who could reach these goals. It should be noted that this is a fundamentally different task conceptually and methodologically than predicting retention in methadone maintenance, for one simple reason. The available data indicate that between 65 and 90 percent of methadone maintenance patients are retained in treatment for 1 year (Szapocznik and Ladner 1977). In contrast, data from several sources suggest that fewer than 20 percent (often fewer than 10 percent) of patients admitted to methadone treatment complete detoxification and remain relatively well adjusted for 6 months (Cushman 1974; Sells and Simpson 1980; Stimmel et al. 1978, 1977). It is important

to note that this is not necessarily an indication of treatment failure, since the majority of methadone maintenance patients show significant decreases in drug use and criminality as well as significant increases in employment and social stability during methadone treatment (Brecher 1972). However, the data do question whether drug free living is a realistic goal and if so, for what proportion of the methadone maintenance population (Sells 1978; Sells and Simpson 1980; Stimmel et al. 1978, 1977). In fact, the small proportion of patients who actually meet the withdrawal criteria, coupled with the number and extent of major methodological problems, leaves little evidence for any truly significant and potentially generalizable patient factor associated with post-methadone adjustment. If there is one factor, it would be the level of pretreatment social adjustment, including employment, family, and social supports (Stimmel et al. 1978). This basic characteristic is apparently a necessary but not sufficient condition for favorable posttreatment adjustment. Several authors have concluded that the oft-cited but seldom defined quality of motivation is a prominent predictor of successful withdrawal (Cushman 1974; Riordan et al. 1976; Stimmel et al. 1978). While this is certainly possible, there is as yet no reliable way of measuring this quality.

A review of the general predictors associated with methadone maintenance indicates that those older patients having less criminality and better social and psychological supports will show better adjustment during methadone maintenance and may have the ability to withdraw and remain drug free following methadone maintenance. However, it is also clear that virtually all drug abuse treatment modalities will do well with this type of patient. It therefore becomes necessary to determine those qualities which differentially predict optimum performance between methadone maintenance and other treatment alternatives. This type of analysis has been pursued effectively by the TCU group using data from 52 treatment programs across the country (Simpson and Joe 1977) and by a Veterans Administration study of drug treatment alternatives within the Philadelphia area (McLellan et al. 1980b). The results from the TCU-DARP study suggest that while considerable variation in a number of general predictors such as race and severity of drug use do not significantly differentiate methadone maintenance from therapeutic communities in terms of the optimum response to treatment, the age and criminal backgrounds of potential patients do distinguish the two treatments. Methadone maintenance seems to do significantly worse with younger, more criminal patients,

while these characteristics are less important in therapeutic communities. These results have, in large part, been confirmed by the VA study although they included the qualities of greater family and employment problems as being particularly unsuited to methadone maintenance. If the nature of these two treatment modalities is considered, these conclusions are at least consistent with clinical experience. Methadone maintenance is an outpatient setting requiring the patient to receive relatively brief periods of treatment within the normal context of his daily living. If a patient has experienced greater criminal activity, has few employable skills and no work history, and/or has few family supports available, it will be particularly difficult for methadone maintenance to be effective. These data suggest that a therapeutic community setting may be more effective for patients with these problems. That type of setting would permit the patient to escape the negative effects of environment and focus upon the drug abuse, criminal, and employment problems that he faces in a private setting.

It must be said that, given the number of studies which have attempted to investigate prediction of success in methadone maintenance, the level of sophistication of these conclusions is disappointing. Although the conclusions are at least consistent with common sense and our clinical experience, they are not confident conclusions, nor have they been derived from a body of carefully designed studies. In fact, much of what purports to be prediction in this field is really a rudimentary, retrospective attempt to differentiate good from bad outcome on a single criterion. This review has emphasized the conclusions of several workers in the field, that different outcome indicators are themselves independent and generally predicted, with varying degrees of power, by different independent variables. Thus, studies which have measured only one outcome variable face serious criticism regarding the generalizability of their findings. This review has also discussed (see Cohen and Cohen 1975; Gottheil et al. 1981; McLellan et al. 1983a; Simpson et al. 1978 for more detailed reviews) the difference between searching through a long list of independent variables for those which are significantly different between those subjects that have done well and those that have done poorly, and performing multivariate analyses of regression, covariance, or discrimination. In the former method, all variables are selected without regard for their relationships to each other, for spurious or coincidental findings, and often

without regard for any theoretical or clinical relationship to the outcome measures. While the use of multivariate analyses and several outcome criteria are not perfect solutions to these problems, they provide the only available methods for conservatively and realistically estimating the nature and extent of relationships among predictors and criteria. This review has concentrated on those studies which have been most carefully designed and carried out--those which have arrived at conclusions which were most consistent with available theoretical and clinical knowledge. It will be important for methadone programs to develop more uniform ways of describing their programs and measuring their patients' status at admission and subsequent evaluation periods. Further, it is imperative that predictive studies begin to implement the appropriate analytic methods, which are now readily available. In this way, future reviews of this subject will arrive at more well defined and confident conclusions.

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CRITIQUE

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In 1966, when I was on the staff at the U.S. Public Health Service Hospital in Lexington, Kentucky, the director of one of the earliest therapeutic communities for narcotic addicts came to speak to our patients about his program. After he finished, someone asked him about this new program, methadone maintenance, that had just begun on a very small basis in New York City. His reply was crisp and succinct. "I think methadone maintenance is a great idea; they ought to give money to bank robbers, women to rapists, and methadone to addicts." Fifteen years later the controversy about methadone remains as alive as ever and, at times, the vehemence of the opinions bears little relation to what is known objectively. At other times, however, thoughtful observers have pointed to the difficulties associated with ongoing maintenance in a calm and logical fashion. Because of these real problems, it may be important to develop as much scientific data as possible about the match between patient characteristics and program type. In trying to so do, however, we need to be aware of the possibility that such scientific endeavors may have only limited impact on the controversy about methadone. As the columnist William Raspberry has pointed out in a different context, "Education is the cure only to the limited extent that ignorance is the disease." To the extent that the controversy about methadone relates less to scientific aspects of maintenance of an addict and more to moral and emotional aspects, the issues discussed here will have less impact on the larger society.

Dr. McLellan's paper, to which this discussion is a formal response, is an excellent job of summarizing most of the relevant studies about patient characteristics associated with outcome. Studies that he has omitted from his survey do not appear to alter his chief findings. Let me start, therefore, by summarizing what those findings are. First of all, Dr. McLellan points out the methodologic problems that cause most of the studies to provide less rigorous data than are necessary to draw hard conclusions. As a result, even the cautious findings he reports must be interpreted with further caution. Age, marital status, and race seem to be the important demographic characteristics relating to program retention. Age (older), race (black or nonwhite), and marriage or a stable relationship all seem to correlate with increased retention and could jointly account for 10 to 20 percent of total variance.

Increased pretreatment criminality, poor work history, use of nonopiate drugs, and greater severity of psychological problems are the major patient background variables correlated with poorer retention and performance during methadone. Taken together, the demographic and background variables may account for 25 to 40 percent of variance in treatment retention or treatment performance.

It was more difficult for McLellan to come to conclusions about factors relating to performance following maintenance because of the small proportion of patients who actually completely detoxified and the many methodological problems associated with attempts to classify this small group. Only about 10 to 20 percent of patients successfully completed detoxification. Of the demographic factors, only age seemed to be relevant to both young, recently addicted patients, and older addicted patients who may have reached a point of maturation doing the test. However, age does not seem to be a major factor in predicting outcome. Socioeconomic status and work history may have some relationship to posttreatment performance but the extent was difficult to determine. Of the treatment factors, length of time on methadone was positively related to the likelihood of withdrawal success and to posttreatment measures of drug use, employment, and crime. Patients who were better able to stabilize on low dosages also seemed to do better. He concludes, however, "even the best combination of these variables cannot account for very much."

If one looks at all the above factors, it is obvious, as McLellan notes, that those patients with the greatest assets and least serious problems show the best performance. Such an observation is hardly surprising since it has been noted in other areas, e.g., prediction of success in psychotherapy. However, McLellan separates out three groups: those patients who would seem to do well in practically any drug treatment modality; those patients who would not do well in any modality; and the middle group of patients for whom choice of modality may be important. In examining studies about this latter group, he finds that therapeutic communities seem to do better with young, multiple drug using patients with worse employment histories, and methadone did better with patients of an older age and lower severity of employment and family problems at admission. In terms of type of drug use, methadone programs had a better outcome with opiate-stimulant abusers, a worse outcome with opiate-depressant abusers, and no difference with the opiate-only group.

Before commenting on the patient characteristics enumerated above, a few methodologic comments are in order. McLellan avoids using the term "random assignment" in his literature review. This omission is hardly surprising since such studies in the drug treatment area are truly rare and, where they have been tried, have been generally disastrous in that the dropout or refusal to enter an unwanted treatment, usually a therapeutic community, has been of such a magnitude that not much was left to measure. Thus, although random assignment may be theoretically ideal, in practice, at least in the drug treatment field, it is so uncommon that it is impractical to waste time bemoaning its absence. Sells (1979) has defended "the utilization of robust multivariate methods that can assess the effects of variations in patient demographic and background characteristics, prior treatment, and other factors that influence outcomes in addition to those attributable to treatment." It may be, however, that the field has been handicapped in the past by the unavailability of appropriate modalities for random assignment. Therapeutic communities and methadone maintenance differ so widely that it is hardly surprising that a true random assignment seems all but impossible to carry out in a democratic society. Random assignment between two outpatient approaches such as methadone and narcotic antagonist maintenance has not been done, probably because of the concerns raised in random assignment to an experimental drug that has not yet been approved by the FDA. If naltrexone does gain such approval, which is widely expected and hopefully can occur within the next year or so, it might then be possible to design studies where the dropout rate is not of such magnitude that it is unlikely that valid conclusions can be drawn.

Another methodological problem omitted was the role of changing patient characteristics over the years. Patients coming onto methadone maintenance in the late 1970s and early 1980s do not in some characteristics appear to be the same patients who came on to such programs in the late 1960s and early 1970s (Kleber 1977).

It is therefore important in looking at patient characteristics to keep in mind this change in patient population. Not only are demographic and background factors likely to be different now than earlier, but aspects of motivation may be strongly different. This may change even over short periods of time. Thus, today when many programs in the Northeast have waiting lists, motivation to remain on the program may be higher than where it is easier to drop

out and come right back in. Studies from different periods of time and different regions of the country may come to different conclusions and lead to a "canceling out" effect. Even less often recognized than change in patient characteristics is the problem of changing programs over the years. The longer a treatment program goes on, the more likely it is that a "silting up" phenomenon will occur in which the program will have more and more chronic users (Penk and Rabinowitz 1978) and the composition as a whole may be less representative of the population of heroin abusers.

In looking at all of the factors that emerge from McLellan's analysis of many studies, what is quickly apparent is that there are no surprises. All of the factors can be explained on clinical grounds, and an adequate rationale could be easily developed for why age or employment status or criminal history are associated with performance, retention, etc. It is not as easy to explain why other factors for which equally compelling reasons could be given do not correlate. This could be a function of methodologic deficiencies or could be a true finding. A further difficulty with interpreting these studies is that clinically one can at times argue for the validity of opposite criteria. Thus, one could make a persuasive case that frequent convictions or increased time in prison would bode well for treatment success because the individuals were obviously unable to be successful criminals, should be tired of such a life, and be more interested in stopping; or, conversely, one could argue that the presence of that history demonstrates the existence of an individual who had so much trouble conforming his behavior to rules and structure that it is unlikely that the program can be successful. One can create similar arguments for a number of factors. An often cited criticism of psychoanalytic theory is that it could explain away a variety of happenings in such a way that true hypothesis testing is not possible. The scientific gathering of data in these studies is supposed to avoid this problem. So why, somehow, are we not convinced? A similar comment was recently made in a lecture by Dr. Parloff in regard to studies on the efficacy of psychotherapy. Even though there have been numerous studies demonstrating such efficacy, to one degree or another, neither the public nor Congress nor the general scientific establishment appears convinced.

Where possible, outside evidence relating to a particular factor may be especially corroborative. Findings that

psychological severity is inversely correlated with retention in treatment and performance during treatment are highlighted by our recent study (Kleber 1981) which found that addicts in the community who had not sought treatment were most easily distinguished from those who had applied for treatment on the basis of psychological severity rather than any other predictive factor. The individual who is less psychologically impaired is better able to function in the community without treatment and, likewise, when he does enter a treatment program, is more likely to succeed.

Another factor not mentioned by McLellan but which might be of great importance once we learn how to accurately measure and correlate peripheral and central levels are the endorphins. The founders of methadone maintenance, Drs. Dole and Nyswander, speculated about the existence of a metabolic deficiency that might require ongoing maintenance (Dole and Nyswander 1965). The discovery of opiate receptors (Goldstein et al. 1971; Pert and Snyder 1973; Simon et al. 1973; Tereneus 1973) and endogenous opiate-like substances (Hughes 1975) raises the possibility that some individuals may need to be maintained on methadone for no other reason than a deficiency of endorphins, either inborn or acquired by prolonged use of illicit narcotics. It may be that relative endorphin levels will turn out to be as important or more important a predictive factor of who does well than any of the demographic, patient history factors, or psychological characteristics cited so far. Even if it does not predict program retention, it may prove to be the crucial variable relating to success after withdrawal. Those people who are able to successfully achieve a drug free state may be those whose endorphin levels return to normal quickly and those who relapse or who are unable to achieve zero dosage may be those individuals whose levels remain depressed for an excessively long period or whose levels, in fact, may never return to normal. Some years back, Resnick et al. (1970) speculated that there might be differences between clients who were appropriate for antagonist treatment and those who were appropriate for methadone maintenance. Individuals best suited for antagonists take narcotics to get high, whereas those for whom maintenance would be best were patients who say that methadone made them normal and enabled them to work better. Although the scale he devised to demonstrate this has not been found to predict success in treatment (Kleber et al. 1974), the concept is an intriguing one. A "normalizing" effect of methadone may be an important factor in treatment and could relate

to the finding that patients with opiate-stimulant abuse do better than those with opiate-sedative abuse. Schizophrenic patients and manic patients may do better on methadone (Watson et al. 1979) while depressed patients may not do as well. Since depression is the most common finding in the diagnostic studies of addiction (Rounsaville et al. 1982), the severity of this might well correlate with dropout rates. In this connection it would be interesting to see whether dropout rates, if they correlate with severity of psychopathology, relate also to program variables such as the availability of sophisticated treatment support over and above the methadone itself. Those programs that are able to offer effective psychotherapy or pharmacotherapy may be able to retain their severely psychologically disturbed clients as well as their less disturbed ones. It is ironic, of course, that methadone programs in general do better with the less disturbed patients, while at the same time the image of methadone programs in some ways is the opposite. Individuals maintained on methadone are commonly viewed not only by therapeutic community advocates but by much of the general public as being dependent individuals who are weak and unable to function in the community in an independent fashion (Brown et al. 1975).

McLellan wisely skirts the issue of motivation since, as he points out, it has not been adequately defined and studied. However, patient expectations which relate to this may be more easily defined, and future studies should investigate this variable. One important reason, after all, for dropping out of a program may be differential expectations between the client and the staff (Williams and Johnston 1972). This can work in both directions. The client may be looking for a program with a free supply of narcotic and minimal demands and structure, whereas the program may have high expectations of significant changes in the patient's lifestyle. Conversely, a client may get in the program, do well, feel that he does not need treatment any more, and drop out earlier than the staff would like because of their fear that the person has not been stabilized long enough to enhance the prospect of long-term success. It should be possible to operationalize these factors and measure them in future studies. It is also clear to clinicians who have had experience with different programs that some programs are relatively loose, and most patient attrition is due to dropout, whereas other programs have high expectations, and patient attrition is primarily due to expulsion. It would be interesting to compare and contrast the characteristics of

patients from both programs as to expectations to see if long-term outcome is significantly affected.

Finally, it is relevant to return to the initial part of the paper and raise the questions again as to the purpose of these studies. It is unlikely that any of the studies will significantly affect whom methadone programs admit. Even with high correlations, it is unlikely that these factors will explain more than half of the variance. Thus, it may be viewed by the community as unfair to exclude any given patients because they statistically look like potential failures. Or communities may feel it is better to keep someone on methadone no matter how badly he is doing because the alternatives are even worse (Jacobs et al. 1979). It is also necessary to keep in mind that these studies have been done on patients in treatment so that their validity for screening untreated applicants may be considerably less. People already in treatment obviously may differ in important ways from those attempting to gain entrance into the program (Snowden et al. 1972). A more relevant use of the data may be related to the last point that McLellan made, the differential impact of methadone versus TCs on certain kinds of patients. His data may be better used to steer patients to more appropriate programs, especially if similar kinds of studies can be done on antagonist programs. For patients who refuse to go to "appropriate" programs, where their characteristics predict greater success, the program administrator is left with the issue of whether to admit poor risk clients to a program at the price of excluding patients with higher probability of success. As waiting lists increase and funds decrease, this may be of more than academic interest, although social policy may never permit it to be put into play.

Perhaps the most useful area for the data reviewed here might be to improve treatment and highlight the needs for new kinds of programs. By examining the kinds of patients who do not do well, program administrators may be able to add to program services that can help their patients, such as tricyclic antidepressants or family therapy. For factors that cannot be changed, such as age, race, previous employment, and previous criminal history, programs will need to try to determine why these variables have the impact they do and possible ways to surmount them.

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DISCUSSION SUMMARY

Fred Altman, Ph.D., and Sidney H. Schnoll, M.D.

There was no disagreement with McLellan's assessment of the strength of the relationships between the various demographic and patient history variables with performance and retention in treatment and posttreatment outcome. McLellan reported that both in treatment and posttreatment the various measures of outcome (drug use, employment, criminal activity, etc.) are essentially independent, based on the finding by both the Institute for Behavioral Research at Texas Christian University and the Drug Dependence Treatment Service of the Philadelphia Veterans Administration Medical Center that there are no more than low to moderate correlations among the measures. (Because of the relative independence of the outcome measures, programs are well advised to provide services directed at each outcome they wish to affect.) It was felt that more studies are needed to look at the factors that bring clients into treatment at a given time and how these factors affect outcome. The discussion of this point was focused on whether retrospective studies are inadequate or whether prospective studies are necessary.

More time was spent discussing the relationship of the pretreatment variables to appropriate treatment than to treatment outcome. There was general agreement that patients with serious psychopathology (regardless of the particular form) do not do well in most of the treatment modalities presently offered. However, there was less agreement regarding the best available alternative for those patients. Some participants felt that long-term, inpatient, drug free treatment was the most appropriate. Other participants felt that the antipsychotic and antimanic effects of methadone may be of therapeutic value to some methadone maintenance patients and that methadone along with other psychotherapeutic agents may preclude the necessity of treatment in a therapeutic community. The finding by the Philadelphia VA group that patients with psychopathology benefit from psychotherapy was mentioned. Both the data and the experience reported by some of the participants suggest that patients with poor employment records and/or serious family problems may be more suitable for treatment in a therapeutic community than in an outpatient methadone program. However, these observations were not unanimously supported.

There was general agreement that further research is needed to determine specific treatment approaches to deal with particular problems brought into treatment and that both clinical trials (micro-studies) and large scale outcome studies (macro-studies) are necessary. There was no resolution of what constitutes an appropriate balance between the two.

CHAPTER 2. TREATMENT CHARACTERISTICS ASSOCIATED WITH OUTCOME

George E. Woody, M.D.

INTRODUCTION

My task for this chapter is to write a state-of-the-art paper on treatment characteristics associated with outcome. The literature on this topic is extensive, and it spans a variety of approaches including pharmacotherapy, counseling, psychotherapy, social work, and family therapy. This paper will attempt to integrate the literature by selecting those aspects that seem to be the most important contributors to outcome. It is important to note that few controlled studies have been done which evaluate treatment characteristics associated with outcome. At present, there is convincing evidence supporting the effectiveness of methadone maintenance and therapeutic communities, and the ineffectiveness of brief detoxification. However, there are few studies which examine relationships between methadone programs or therapeutic communities that are operated according to different styles or staffing patterns, and outcome. Similarly, there are few studies comparing types of treatments offered within these programs and outcome. Thus, much of this paper consists of impressions formed from treating patients and from reading the available literature. These studies may provide leads which can be used to explore and define specific characteristics of those treatments that are known to be effective and are associated with positive outcome.

I would like to start the paper with two general impressions, then move on to services and treatments that are used in most clinics, and finish with descriptions of more specific treatments aimed at special patient populations.

GENERAL IMPRESSIONS

First, treatment programs for narcotic addicts (and my main reference point is methadone programs, although I am thinking also of therapeutic communities, detoxification, and drug free programs) all seem to use a combination of support and structure. In this sense, they may resemble adolescent treatment programs more closely than outpatient

clinics serving primarily neurotic patients. Psychiatrists who enter this field from residency programs which emphasize outpatient psychotherapy can easily be insensitive to the need for incorporating structure into the treatment program. The structure used by most programs includes explicit rules for behavior (with suspension often being a consequence for infractions), mandatory treatment sessions, routine urine testing, and taking medicines under direct supervision. The degree to which structure is emphasized may vary considerably between programs. Historically, the amount of structure required in psychiatric treatments has been noted to be inversely proportional to the ego strength of the patient. Thus, Kleber et al. (1981) findings that addicts' ego strengths lie between the severe impairments seen in psychotics and the mild impairments seen in neurotics are particularly interesting when viewed in the context of the support provided by treatment settings used for addicts. A friend once said that he thought addiction treatment resembled a situation where one was pushing a patient with one hand but holding him up with the other. This analogy does not strike me as too far from the kind of balance between structure and support that clinicians find themselves providing in outpatient methadone programs.

The second general impression is that addicts are quite diverse, especially when viewed psychiatrically. The findings of Kleber et al. (1981) document this thoroughly. Although addicts share the common trait of repetitive, compulsive drug use and have a strong tendency to express themselves via behavioral problems, they also can have a wide range of psychiatric problems, and with a fairly high frequency. Kleber's group found that 85 percent of a sample of 750 addicts had experienced a diagnosable psychiatric illness, in addition to addiction, at some time in their lives. Especially common were the various types of depression (particularly major depressive disorder), antisocial personality, and alcoholism. Less common, but not infrequent, were anxiety disorders, hypomania or bipolar II illness, and labile or cyclothymic personality disorders. In addition, the addict's personal circumstances can be diverse. Some are employed, even upon entering treatment, some are married with children and have responsibilities to meet, some are about to go to jail, some have serious medical problems, etc. This heterogeneity of addict patients, particularly the diversity of their psychiatric problems, is a newly documented reality and carries with it treatment implications. These implications comprise the last part of this paper.

BASIC SERVICES PROVIDED IN METHADONE PROGRAMS

Types of Staff

The major portion of treatment in most programs is carried out by drug counselors. Drug counseling is a treatment that focuses on identification of specific needs and delivery of concrete services. Generally, counselors focus on external factors as opposed to internal or intrapsychic processes. Examples of such factors are paying attention to the methadone dose, writing letters to court, intervening in acute crisis situations, explaining the rules and routines of the clinic, evaluating patient requests for take-home medication, or referring patients to physicians for evaluation of medical or psychiatric problems. Counselors monitor certain important signs of patient processes such as urine test results, signs of psychological adjustment, and legal or employment status. Counselors also monitor the patient's records for compliance with the Food and Drug Administration (FDA) and Joint Commission on Accreditation of Hospitals (JCAH) standards. In some programs counselors take turns collecting urine samples or perform clerical work such as answering phones. Counselors may see patients individually or in groups. Counseling services usually are given once per week, though this can vary. Some counselors have up to 50 patients at any one time, but 35 is a more workable number. Approximately 40 percent of the counselor's time is spent monitoring records and attending clinic meetings, with the rest spent in direct patient contact.

Counselors' backgrounds vary widely. Some are exaddicts without a high school diploma, and others are college graduates. There have been debates in the literature regarding what type counselor is the most appropriate. One study compared the outcome of patients who had exaddict counselors with those who had non-exaddict counselors vs patients who had two counselors, and found no difference in outcome (Longwell et al. 1978). Some have questioned the efficacy of counseling, stating that there are no data proving that counseling adds anything to methadone treatment itself (Desmond 1979). However, those who have tried to study the efficacy of counseling have been unable to establish an appropriate control group because patients assigned to the control group all seemed to need some form of counseling; thus, it was impossible to administer methadone and withhold the kinds of services that the counselor provides (Senay et al. 1973).

In addition to counselors, programs usually have at least one social worker (MSW) who is familiar with the social resources in the community and who can help counselors with patients who have problems related to housing, public assistance, disability, or the legal system. A nurse practitioner can be extremely useful in diagnosing and treating routine medical problems, in referring patients with more complicated illnesses to medical specialists, and in doing routine physicals including drawing blood.

Very important in the overall structure of treatment programs is available physician time. Many programs have very limited physician coverage, and this makes it difficult to respond to the more complicated medical and psychiatric problems that the addicts have. There is really no evidence to document the efficacy of various physician staffing patterns; however, a reasonable amount of time is at least a half day, 5 days a week, for a treatment program which treats approximately 300 patients.

The need to maintain high quality records is becoming more and more important, especially in view of the new FDA and JCAH requirements. The need for the consistent and systematic charting that is necessary to fulfill these regulations probably requires the help of a medical records technician who can organize and operate a system that will inform counselors when treatment plans, annual evaluations, and discharge summaries are due, and who can periodically audit charts for compliance with the regulations. Other necessary personnel are clinic secretaries, nurses, or pharmacists to dispense methadone and keep narcotic records, and guards to ensure order and maintain smooth traffic flow at busy times. Some clinics hire one or two people to collect urine samples; others have counselors take turns with this often unpopular but necessary duty.

Maintenance of Staff Morale and Program Coordination

Addicts can be very demanding, hostile, and refractory to treatment. It is important that the staff have realistic treatment goals, that they are protected from the more severe behavioral problems of patients, and that they develop a coordinated approach to patient management. Coordination is essential because addicts can be highly manipulative and will try to pit one staff member against another in order to accomplish their own ends.

Several things can be done to achieve these goals. First, written policies explaining rules of conduct with specific penalties for infractions will help staff deal with patients, and will also inform patients exactly what to expect if they act in nontherapeutic or destructive ways. It is important to have penalties that vary according to the offense. For example, fighting should lead to a longer suspension than disruptive behavior; carrying a dangerous weapon such as a firearm should result in a very long, perhaps permanent suspension. These written guidelines should be posted. The process of specifying and posting rules will also protect employees from becoming an undue focus for patient anger. It is much safer to tell the patient, "We have no choice but to suspend you because you broke the following rule," than to say, "I am suspending you for 1 year because...." In the second example the suspension is made by one individual while in the first it is in accordance with a larger agenda that was constructed by a group, thus making it harder for the patient to focus his or her anger on one person.

Second, regular staff meetings with specific agendas are necessary to maintain staff coordination. Written policies regarding management of take-home doses, medication changes, the charting of maintenance procedures, management of intoxicated patients, and other daily aspects of treatment will help this coordination process. It is helpful to compile the important policies and procedures of patient management in a booklet that each staff member can use for reference and guidance in daily activities.

Third, it is important to convey a personal sense of interest and involvement in the treatment process. This quality may be advanced by having regular inservice training sessions in which topics of current interest are discussed with special attention to giving staff feedback on all projects done in the clinic. The maintenance of a consistent level of interest and involvement by senior staff in ongoing patient care probably acts as a model for junior staff and can have a positive effect on their morale.

It is important to be sensitive to staff attitudes toward methadone. A survey done by LoSciuto et al. (1979) suggests that counselors often have mixed feelings about the use of this narcotic substitute. The presence of these feelings can be observed in affective reactions to methadone maintenance. Examples are reflected in statements such as: "Methadone is not good for people and they

should get off it as soon as possible"; "High doses are bad"; or, "Long-term maintenance is wrong." These feelings must be modified, especially in cases where the patient only does well when on a high dose, or is totally unable to detoxify successfully.

BASIC TREATMENTS: MAINTENANCE AND DETOXIFICATION

Maintenance

The most widely used heroin substitute is methadone. Patients being treated with methadone must ingest their daily dose under observation 6 or 7 days per week for the first 3 months. After that time, they may be placed on reduced observation schedules. Guidelines for these schedules are outlined in the FDA regulations. The contingencies that are required by FDA regulations for the dispensing of take-home doses probably act as motivators for positive therapeutic progress, as shown by Stitzer et al. (1977). Contingency contracts can also be used to increase motivation in treatment. Programs often have patients who are doing poorly (using drugs, not trying to obtain work) in spite of the best therapeutic efforts of staff. Such patients can be selected for a treatment contract which specifies that certain goals must be achieved within a certain period of time as a requirement for continued maintenance treatment. We find that about half of patients put on these contracts will meet them. Care must be taken in selecting patients for contracts and in setting goals so that the patient can be reasonably expected to attain the goals. All staff must avoid mixing anger or frustration over lack of patient progress into the contracting process. Patients with significant psychiatric problems may have more trouble meeting the terms of a contract than patients with behavioral problems that are uncomplicated by other psychiatric illness.

There has been considerable debate over whether patients need high doses (more than 60 mg) or whether they will do just as well on lower doses (50 mg or less). Several studies have explored this question, and the conclusion seems to be that patients can do well on any dose, that there are many variables which influence outcome, but that, all things being equal, patients on high doses use less drugs and tend to do better than those on low doses (Jaffe 1971). Thus dose can be important, but for most patients it is only one of many variables that influence outcome. In our program we use dose to improve outcome in

patients who are receiving moderate to low doses and who are regularly using opiates. We have found that about half of these patients will stop using illicit opiates if their doses are raised to the 60-80 mg level.

Recently, much work has been done on other substitution therapies, mainly l-a-acetylmethadol (LAAM). It appears that LAAM is not as acceptable to patients as methadone, since most studies comparing the two drugs show that the initial dropout rate is higher with LAAM (Ling et al. 1980). However, patients remaining on LAAM appear to do as well as patients who are stabilized on methadone. Propoxyphene has also been used as a maintenance drug, but it does not work nearly as well as methadone (Woody et al. 1981). Buprenorphine is a new opiate-like drug that tentatively appears to produce less physical dependence than methadone, and which may eventually be used for maintenance treatment. It is now undergoing limited clinical trials (Jasinski et al. 1978).

Detoxification

Most addicts try to detoxify, either on their own or with the help of programs. There is good evidence that brief detoxification is of little benefit, except perhaps insofar as it relieves immediate pressures. The best results with detoxification appear to be obtained by patients who enter therapeutic communities following detoxification or who slowly decrease their methadone dose after a period of treatment in which they show signs of improvement such as having clean urines, keeping regular appointments with counselors, showing psychological stability, obtaining work, and having family support systems. Studies by Stimmel et al. (1977), and others, have shown that a portion of methadone treated addicts who meet these criteria can successfully detoxify. Senay et al. (1977) have recently shown that a very gradual dose reduction (no more than 3 percent per week) is superior to a more rapid reduction scheduled for patients who wish to detoxify.

Naltrexone treatment is sometimes helpful following detoxification. Naltrexone is one of several narcotic antagonists. These drugs block the effects of opiates but have little or no psychotropic effects and do not produce dependence. They appear to be a valuable alternative to maintenance treatment for a small portion of addicts. Some patients who have not done well on methadone or in therapeutic communities have been treated successfully

with naltrexone, but the acceptability of naltrexone is much less than methadone (Julius 1979).

Clonidine and more recently lofexidine have been reported as useful adjuncts to detoxification (Gold et al. 1980; Washton, personal communication, 1981). Clonidine is the first nonnarcotic drug to effectively suppress the symptoms of narcotic withdrawal, and thus it is interesting both pharmacologically and clinically. Clonidine may be especially useful in increasing the number of patients available to take naltrexone because it allows patients to be detoxified with relative comfort in much less time than is usually needed.

Legal pressure is a powerful variable that has been shown by both McGlothlin et al. (1977) and Vaillant (1974) to have a positive influence on outcome. It has been studied most extensively when combined with drug free approaches such as a therapeutic community. It can motivate patients to get jobs and abstain from illicit drugs. Its effectiveness is probably related to the rigidity and wisdom with which it is applied. Some patients will not respond to legal pressure, and it can have adverse effects. An example would be remanding a patient to jail who has been doing well for several months on the basis of one missed appointment or a single "dirty" urine. It is probably most effective when used in combination with another treatment such as a therapeutic community, methadone maintenance, or naltrexone.

ADDITIONAL TREATMENT AIMED TO IMPROVE UPON THE ROUTINE SERVICES

The above comments, with a few exceptions, have dealt with standard aspects of treatment. This section will discuss how the individual patient variability mentioned earlier in this paper can offer an opportunity to further refine these treatments.

The very existence of this variability underscores the importance of evaluating patients for problems in several areas. The assumption made here is that we are treating individuals, all of whom share a common problem with drug abuse but who are human beings, with a variety of needs and problems. Important areas of potential disability to be evaluated are: (1) drug use (including alcohol), (2) psychological problems, (3) family problems, (4) vocational adjustment, (5) legal problems, and (6) medical

problems. McLellan et al. (1980) have developed an instrument that evaluates the need for treatment in each of these areas called the Addiction Severity Index. It is a test that can be administered in 20 minutes by a technician and has been shown to evaluate reliably the need for treatment in each of these six areas. We have used this instrument in our program for both initial and followup evaluations. Patients who have moderate to marked impairment in specific areas at intake are referred by a treatment planning team to personnel who have expertise in dealing with that particular area. For example, the person who has problems with employment is referred to the vocational specialist, the patient who has a serious medical problem is referred to the nurse practitioner for evaluation and perhaps referral to a medical subspecialty clinic, etc.

An area of special interest to us is the psychological problems. Treatment outcome studies done by McLellan et al. (1980) and presented in this volume (part III, chapter 1) have shown that psychological adjustment correlates with outcome in other areas; thus, successful treatment of psychological problems should help not only that particular area, but also produce extended effects in the areas of drug use, employment, and vocational and legal adjustment. Because this area is important and because we have a special interest in it, the remainder of this paper will discuss treatment aimed to reduce the psychological problems seen in addicts.

Psychotropic drugs are often helpful in treating psychological problems. The benzodiazepines can relieve anxiety; the antidepressants may help patients with major depressive disorders; hypnotics or the sedative type antidepressant agents can be used to treat insomnia; and antipsychotic agents are helpful for patients with schizophrenia. Few systematic studies have been done to evaluate the success of these various pharmacological treatments in opiate addicts. One study recently completed by Kleber et al. (1981) showed that imipramine when used with methadone for the depressed addict did not appear to improve upon routine treatment services. However, there is evidence that doxepin, a sedating type antidepressant, is useful for methadone-maintained addicts (Woody et al. 1975; Titievsky et al. 1982). Almost all clinicians feel that special care should be taken when prescribing benzodiazepines, especially diazepam, because of its abuse potential, and that most sedative hypnotics should not be used in this population. Antipsychotic drugs which come in a

liquid form can be mixed with the daily dose of methadone, thus assuring compliance for those addicts who do not take the medication as prescribed. Methadone itself has anti-anxiety and antipsychotic properties (McLellan et al. 1980); thus, merely stabilizing a patient on methadone is often sufficient to reduce an associated psychiatric problem to tolerable levels. Use of ancillary psychotropic medicines should probably be avoided until one is certain that the patient is reasonably well stabilized as evidenced by a lack of opiate withdrawal symptoms.

Psychotherapy is another area of special interest to us in the treatment of psychological problems. Previous attempts at psychotherapy with addicts had only limited success, due in some part to the inability of patients to abstain from drugs and keep regular appointments. However, the advent of methadone maintenance has provided an opportunity to test the efficacy of psychotherapy for these patients. Several years ago, our program collaborated with Stanton et al. (1981) in a study evaluating the efficacy of structural family therapy when combined with methadone treatment. This study, which has been described in the literature, essentially found that the family therapy patients did better than those receiving counseling alone. This form of treatment may be particularly helpful in patients with severe family problems; however, it is important to emphasize that there are often considerable practical difficulties in getting families together for family therapy. Thus, this treatment often requires that the therapist spend considerable energy arranging for the treatment sessions. However, when the family becomes engaged, the treatment can be helpful.

Individual psychotherapy is somewhat easier to deliver and may also be helpful. We are in the process of completing a program designed to test the efficacy of two different forms of psychotherapy when combined with drug counseling for patients being treated on a methadone program, and the remainder of this paper will focus on this study, including presentation of data that seem particularly interesting and relevant. This study involved random assignment of patients to one of three treatment conditions: supportive-expressive therapy plus counseling; cognitive-behavioral psychotherapy plus counseling; or counseling alone.

Supportive-expressive therapy (SE) is an analytically oriented, focal psychotherapy modeled after that described by Sifneos (1962) and Malan (1963). It aims to help the

patient identify and work through problematic relationship themes. The therapist identifies these themes via the relationship with the patient (transference), or according to what the patient says about other important relationships such as those with spouse or other family members. Special attention is paid to the meaning that the patient attaches to drug dependence. For example, a therapist might have a patient who denies having any problems. The patient keeps appointments out of "curiosity" or because he thinks he "ought to," but maintains that things are going well in spite of being unemployed and having an unstable living situation. When he has a problem with his girlfriend, he refuses to discuss it, misses several sessions, and uses drugs, then asks his counselor to have his methadone increased. In this case, the therapist identifies the patient's denial as it appears in the transference, in the relationship with his girlfriend, and in his drug use. The therapist works with the patient, aiming to diminish the denial. If the therapist is successful, treatment should help the patient address his problems more directly, and thus increase the likelihood of finding better solutions than using drugs to solve life problems. Part of SE training also includes the awareness of countertransference issues including their recognition, their use as signals of important relationship themes, and how to avoid responding to them in ways that would interfere with the therapeutic process.

Cognitive-behavioral therapy (CB) is a treatment that aims to identify and change false beliefs, unhealthy moods, and problematic behavior. It is a treatment that has been developed by Dr. Aaron T. Beck (1976) and has been shown to be effective for treating certain types of depression. Dr. Beck and his colleagues have found that depressed patients often have false and negative beliefs, such as seeing themselves as helpless or worthless, and that these beliefs can have a profound influence on mood. Reversing these false beliefs can significantly improve mood. For example, when a person is withdrawn, depressed, and feels that he is worthless and cannot succeed at anything, a CB therapist, having identified these false beliefs, attacks them actively and directly, aiming to show the patient how and why they are untrue. If the therapist succeeds in reversing them, the patient's mood brightens and the associated social withdrawal decreases. During CB therapy, the patient may be required to do "homework" such as recording daily activities and thoughts or deliberately altering certain behaviors. Some false beliefs commonly seen in narcotic addicts include, "I'm a junkie, I'll never get

better," or "I can't possibly feel good without drugs." The CB therapist identifies these beliefs and works actively with the addict to change them.

As seen in the above descriptions, these therapies differ from counseling in that their emphasis is on intrapsychic processes rather than external events and concrete services. The therapists in our project were either Ph.D.s or M.D.s who were finished training and had experience doing psychotherapy that ranged from 2 to 30 years.

After being assigned to one of these three treatment conditions, the patient was given a brief explanation of the kind of treatment he would receive. The importance of keeping regular appointments was emphasized at this time. All patients were required to have at least three meetings with their counselor and therapist (if they were assigned a therapist) within the first 4 weeks. These mandatory sessions were required to make sure that all patients had an opportunity to gain some familiarity with the treatment conditions. After these three sessions were completed, patients were encouraged but not required to keep appointments. Those patients who were assigned a therapist had an opportunity to continue with that person for 6 months. Our analyses of overall treatment results show that patients receiving counseling plus psychotherapy did better than those receiving counseling alone. Given our findings that psychotherapy can be an effective adjunct to methadone maintenance for the general population, and because previous reports have indicated that greater severity of psychological problems can have a serious impact upon the outcome from methadone maintenance (Szapocznik and Ladner 1977), we undertook a study designed to evaluate these factors in combination. Because psychotherapy is aimed specifically at psychiatric problems, we hypothesized that there might be a differential effect of psychotherapy plus counseling vs counseling alone on patients with marked psychiatric problems.

To examine this hypothesis, we examined data on the first 62 patients to complete therapy and divided them into four groups based on ratings of psychiatric symptoms that were obtained at intake. The measures used to make these subdivisions were the Beck Depression Inventory, the Maudsley Neuroticism Scale, and the psychological scale of the Addiction Severity Index. Because these pretreatment measures provided a valid estimate of general psychological status, we selected two extreme groups: those showing

high levels of symptoms and clear, if presumptive, evidence of psychological problems (N=21), and those showing low levels of psychiatric symptoms (N=21). A total of 42 patients were included in these four groups, leaving 20 patients who are in the midrange, and who were not included. We selected only the extremes since we felt that this method would give us the best chance to test our hypothesis.

We then subdivided these groups on the basis of their treatment assignment into high severity counseling (N=10), high severity therapy (N-11), low severity counseling (N=11), and low severity therapy (N=10). No distinction was made between the two psychotherapy groups because differences in outcomes between them were small. A summary of the psychological test results for these four groups is presented in table 1. As seen, the groups are distinctly different in terms of the amount of psychopathology. The number of DSM III diagnoses (other than drug dependence) for these groups is seen in table 2. About 76 percent (7 of 10; 9 of 11) of the patients in the high severity groups had a DSM III Axis I diagnosis, while only about 28 percent (2 of 10; 4 of 11) of the low severity patients were given DSM III diagnoses other than drug dependence. Axis II diagnoses were equal between the groups and were almost always antisocial personality disorder.

We examined pre- to post-therapy improvement for patients in each group using the ASI. The ASI severity scores and other related items are presented in table 3. As seen, the high severity counseling group showed improvement only in areas clearly related to drug use. One might expect this since the patients were on methadone. The low severity counseling group demonstrated significant improvement in several areas, indicating the counselors are having a distinctly greater impact on this group than on the high severity patients. Conversely, the high severity therapy group demonstrated significant improvement in several areas, equal to that seen in the low severity counseling group. The low severity therapy group is also making considerable improvement, perhaps of greater magnitude than the low severity counseling group.

The mean methadone doses for each group are seen in figure 1. There was a significantly ($p =<.01$) higher mean methadone dose for the high severity counseling than for any of the other three groups. The low severity therapy groups, and the high severity therapy and low severity counseling groups, received comparable intermediate dosages. The

Table 1. Psychological status of the four groups at the start of the survey

	High severity counseling	Low severity counseling	High severity therapy	Low severity therapy
N	10	11	11	10
Beck	18	10	21	9
Maudsley-N	41	24	37	20
Shipley IQ	100	103	96	104
Shipley CQ	80	87	80	94
Addiction Severity Index Psychological Severity	5.1	2.7	5.6	.3

Table 2. DSM III diagnoses

	High severity counseling	Low severity counseling	High severity therapy	Low severity therapy
Patients with/ Axis I diagnosis	7/10	2/10	7/11	4/11
Examples	Bipolar affective General anxiety Chronic affective	Bipolar affective Single depressive	Bipolar affective Chronic depressive General anxiety	Bipolar affective Manic disorder General anxiety
Patients with/ Axis II diagnosis	7/10	5/10	9/11	7/11
Average Axis IV (stress severity)	4	4	3	1
Average Axis V (highest function)	4	4	4	2

Table 3. Pre- to posttherapy (7 months) improvement

	High severity counseling		Low severity counseling		High severity therapy		Low severity therapy	
N	10		11		11		10	
Medical Severity	3.1	2.4	1.7	3.2	2.5	3.5	1.8	0.7
Days Medical Problems	4	2	2	4	3	3	1	1
Employment Severity	4.5	4.6	5.1	+3.2	3.8	3.0	3.9	+2.7
Days worked	9	11	10	13	7	10	9	13
Money earned	272	306	242	+380	309	+482	318	*523
Abuse Severity	5.7	+3.8	3.8	*1.4	4.9	+3.0	4.0	*1.4
Days drunk	4	2	2	1	3	2	2	+0
Days opiate	6	3	10	*2	5	2	8	+3
Days nonopiate	10	8	4	2	7	+3	3	1
Money for drugs	430	*190	164	*47	344	*65	188	*8
Legal severity	3.1	3.0	4.5	+3.1	2.8	+0.7	2.0	+0.8
Days crime	6	3	10	+4	5	+0.8	1	0.4
Illegal income	216	181	506	+300	186	*43	166	*10
Psychological Severity	5.1	4.8	2.7	1.8	5.6	+3.0	2.5	+1.0
Days Psychitric Problems	17	13	8	3	15	+8	4	+1.0

* = $p < .01$
+ = $p < .05$

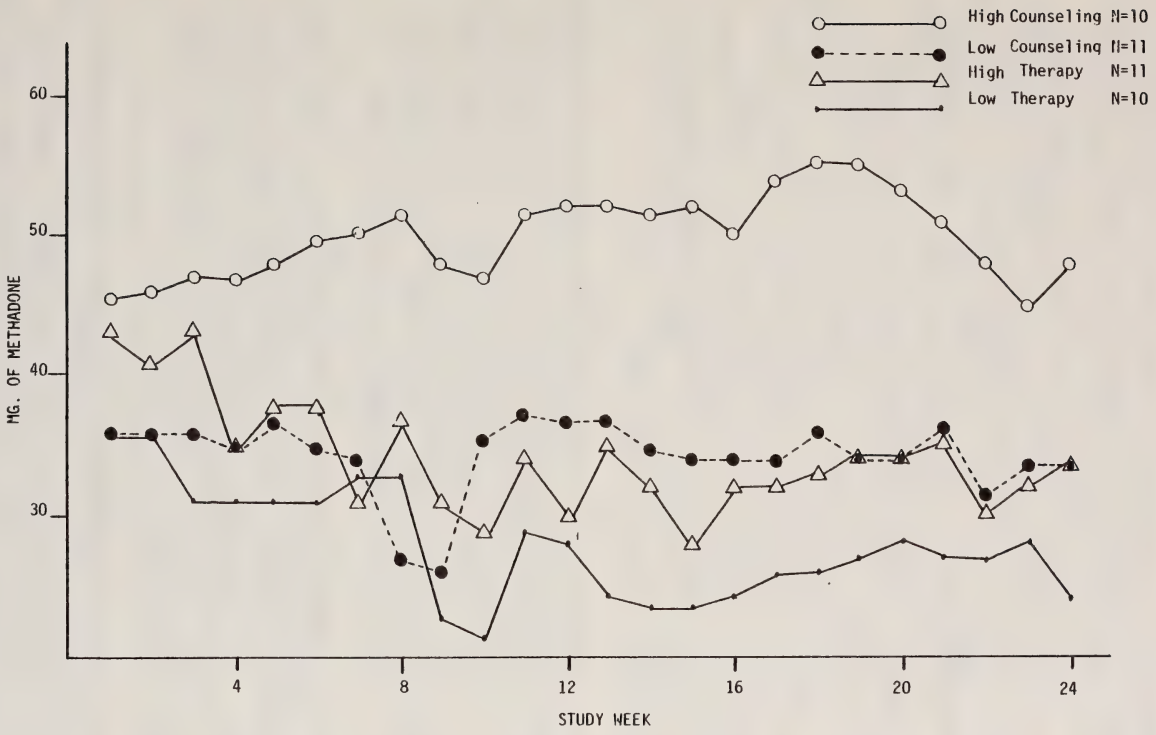

Figure 1. Mean methadone dosage by group

mean dosage of the high severity counseling group is significantly greater than the other groups in both a statistical and clinical sense.

In addition to methadone we often prescribe ancillary psychotropic medications for temporary symptomatic complaints of depression, anxiety, or insomnia, as mentioned earlier. These medications include doxepin, oxazepam, and flurazepam of chloral hydrate. The percentage of subjects who were prescribed ancillary psychotropic medication is seen in figure 2, and the data show a pattern identical to the methadone doses. These data indicate fewer symptoms and a corresponding reduction in need for medication among both groups of therapy patients and also among the low severity counseling patients. Urine drug screening results are seen in figure 3. The high severity counseling group has significantly ($p =<.05$) more "dirty" urines than either of the other three groups, who have about the same frequency of positive urine. Nonprescribed benzodiazepines were counted as a positive urine in this category and this may mask slight differences between groups because one dose of a long acting benzodiazepine can be detected in the urine for 3-5 days.

As seen, patients with high levels of psychiatric symptoms use more drugs (both prescribed and illicit) than patients with low levels of symptoms. This finding is especially clear in figures 1, 2, and 3, where high severity therapy patients have higher methadone doses, use more ancillary medications, and have more drugs in their urine than low severity therapy patients. These same relationships are seen in the high and low severity counseling groups.

Similarly, the psychotherapy patients appear to be doing better than patients receiving only counseling. This is particularly evident when we examine the high severity groups. In these very difficult patients, the counselors seem to be having little impact, whereas the therapists are having an impact in several areas, including the ASI rating of psychological severity.

Further analyses are needed to explore the factors that may contribute to these results. Nonspecific factors, the opportunity to meet with two helping people rather than one, and the fact that the psychotherapy patients received more total therapy time must be explored as possible contributors to these results. However, these findings do

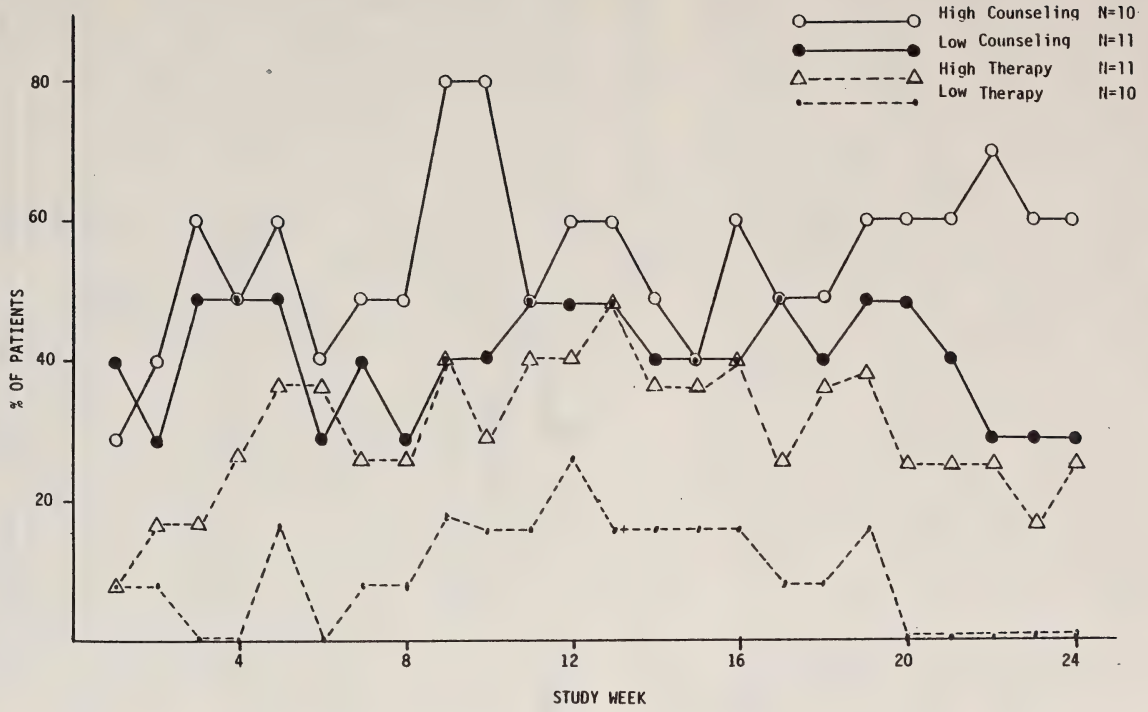

Figure 2. Patients receiving ancillary medication by group

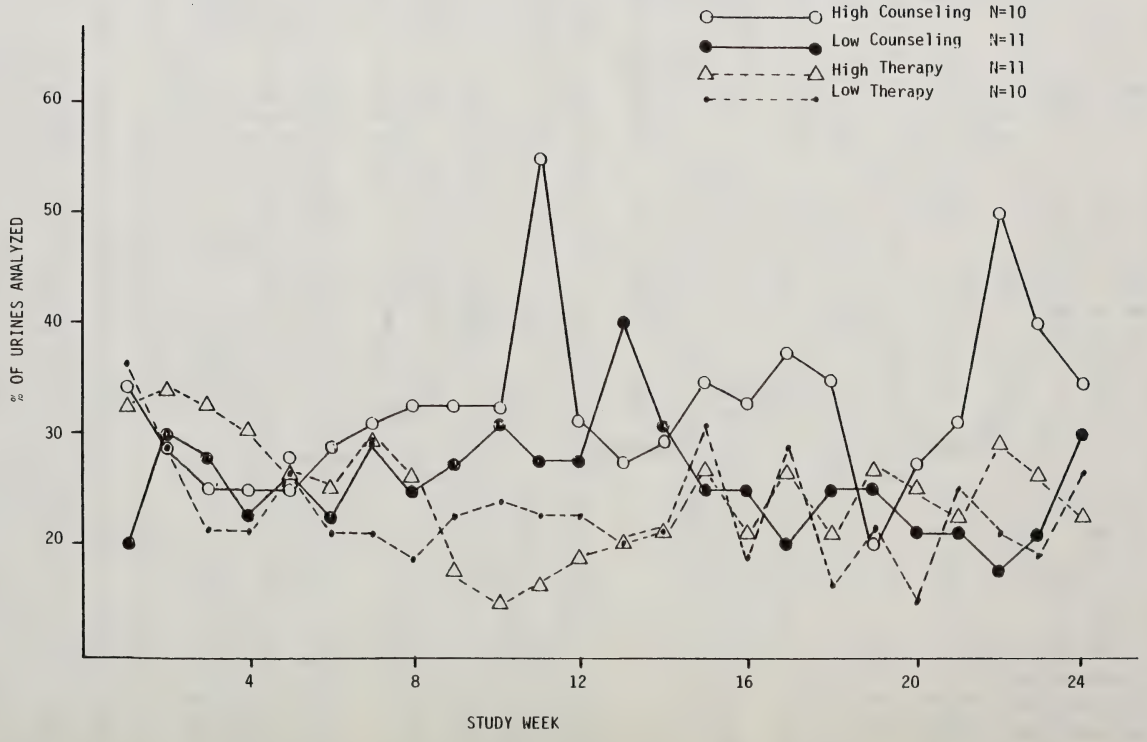

Figure 3. Positive urines by group

provide evidence to suggest that professional psychotherapy may add something to ongoing treatment services, particularly for patients with high levels of psychiatric severity. These patients comprise perhaps 20-30 percent of all patients in methadone treatment programs; thus the addition of professional level psychotherapy to ongoing treatment services may provide a useful alternative for a significant minority of patients who are engaged in methadone programs. This same finding probably would also apply to patients receiving drug free counseling or naltrexone and possibly could be tested in a therapeutic community setting. A very practical application of these findings would be to use the ASI to identify patients with significant psychological problems, and then to assign them to a counselor plus a professional therapist. One or two therapists working one-fourth to one-half time in a program could provide a valuable and economical addition to routine counseling service in this way.

CONCLUDING REMARKS

This overview reflects my view of the various treatment variables that may influence outcome with a special emphasis on psychotherapy and psychological illness. The interface between a psychological approach and the need for structure and rules must be recognized when psychiatric problems are to be addressed. The existence of written clinic policies and standards of patient behavior is helpful in defining this interface. Under a combination of structure and support, it is possible to approach patients psychologically without compromising the need for rules, thus avoiding the trap of focusing on one end of this balancing rod to the exclusion of the other. The principles that seem to emerge from the literature, combined with our experience, are similar to those found in general medicine. First, make an accurate diagnosis by taking into consideration all the known areas of potential disability. This is done with the ASI. Then use this information to match patients with specific treatments that are aimed to reduce problems in specific areas. All of this diagnostic work and patient matching is done within a treatment setting that includes rules of behavior, the provision of general services by trained supporting personnel, and support services available and functioning in a coordinated manner.

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CRITIQUE

Edward Senay, M.D.

The charge to critique the preceding paper is sufficiently broad to require a critic to define how he or she understands such a charge. I define it as a charge to examine critically studies relating varieties of treatment methods which have been applied on a national scale for an extended period of time to changes in behavior measured predominantly in persons with established opioid dependence, assuming control over variation in the characteristics of those treated.

Given this definition, aversive therapy for opioid addicts, meditation, acupuncture, and the like would not qualify for review because they have not been carried out on a national basis. This definition determines that the variance attributable to client characteristics, age, sex, ethnicity, length of addiction, severity of criminal involvement, and employment history, all with compelling evidence of impact on the treatment process, would not be considered. This definition also appears to be at variance with that of Dr. Woody, who apparently understood the charge as a stimulus to describe the characteristics of an ideal program. He begins his paper by expressing a conviction that all treatment programs provide support and structure. He also observes, quite properly in my opinion, that addicts are heterogeneous. But this latter observation is outside the charge as I have defined it.

Dr. Woody's prescription for programs--written Standard Operating Procedures, regular staff meetings, formal in-service training programs, availability of a mental health consultant, optimal caseload size, record keeping of sufficient quality to satisfy FDA and JCAH requirements--expresses my biases in the matter in every regard. But I believe that they are tangential to the basic charge of examining variations in support and in structure as they relate to treatment outcomes.

After defining the charge, I believe it important to distinguish between levels of analysis. The drug abuse field has made many attempts to evaluate its effectiveness but has not done so at the level of hypothesis testing research. Explicit hypotheses concerning treatment-related variables have not been elaborated and

studies of the treatment process employing random assignment, appropriate blinds, etc., have not been carried out. Until we have such studies, we cannot say that based on scientific evidence, methadone maintenance programs of type A are superior to methadone maintenance programs of type B. But this somewhat discouraging view does not leave us with the impossible job of evaluating the untested claims of partisans of one facility or of one treatment modality. There is a middle level of systematic observation and the use of statistical techniques which partially compensate for our lack of well controlled studies. This middle level has been well exploited by the field.

Dr. Nash (in press) has reviewed the major studies of treatment of opiate addiction and concludes that desirable treatment changes are associated with methadone maintenance programs and with therapeutic communities. He points out that we are unable at this time to decide whether the changes are due to treatment for a variety of methodological reasons.

Dr. Sells' group at TCU (1974) created a treatment typology which might permit us to refine our evaluation attempts, but we do not have studies in which there has been random assignment to the varieties of methadone maintenance programs he describes. Dr. Sells' typology of methadone maintenance programs defines two main types; these differ principally on the variable of structure, with one type being relatively less demanding of program compliance than the second type. Dr. Sells' analyses suggest some superiority for the less structured type, but this is approximate. There is no ethical or logistic barrier to NIDA's funding of a study in which random assignment to these types could occur. The argument against the use of untreated controls is compelling, for ethical and political reasons. I don't believe that we can use untreated control groups, but the comparison between maintenance types could be carried out given sufficient investment by the leadership of the field.

Maddux and Bowden (1972), among others, have pointed out the methodologic flaws in our evaluation techniques. One major flaw is the use of remaining samples. As they demonstrate elegantly, the data on employment can be analyzed with quite different results from those usually obtained if the number of original study entrants is used as a denominator and if employment rates among untreated addicts are compared with in-treatment rates of employment.

Community attitudes toward a particular treatment modality can affect treatment outcome in major ways. Our national experience with Darvon-N in which community attitudes both for and against methadone maintenance strongly influence acceptability and compliance is an outstanding example. The implication for the future is that this variable must be assessed and integrated into research designs.

The background of staff and their attitudes toward a particular treatment are also variables which can have powerful effects on outcome studies (Brown et al. 1972; Szapocznik and Ladner 1977). Desmond (1979) has reviewed critically the contribution of counseling to outcome in methadone maintenance programs. He concludes: "The few studies which have been reported seem to suggest that counseling does not significantly change treatment outcomes as measured by the usual indications of illicit drug use and retention in program." Desmond quite properly cites the methodologic flaws in existing studies but then falls into a common error, namely, if existing work is flawed so that we cannot decide that a given treatment is effective, then we cannot decide, as he appears to, that the treatment or procedure is ineffective. Bad designs permit no inferences.

A key variable in the question under discussion is compliance. We do not measure this variable because we don't know how to measure it. Any scientific examination of the relationships between treatment and outcome will have to come to terms with this measurement. If two subjects identical in drug abuse patterns, age, sex, severity of psychopathology, etc., enter a program, but one engages while the other doesn't, comparison of the two on outcomes is confounded, and until we can measure such variation we will never have the kind of data we would all like to have.

This particular passage leads me to the major part of my critique. We should have studies, as we have, of the magnitude of those conducted by Sells, Burt Associates, etc., but we also need smaller fine-grained studies to supplement these large efforts. NIDA's evaluation effort, while equal or superior to that of any previous large human service delivery system in history, has been deficient in this respect. All the money has been placed in large-scale, long-duration studies. We should make up for this deficit in the future with a strategy which recognizes the need for micro-level as well as macro-level evaluation.

A key question, given the large cost difference per patient year, is to compare methadone maintenance programs with therapeutic communities. I know of no study in which addicts have been randomly assigned to one or another of these modalities and then followed for appropriate periods. We attempted this in Illinois but discovered that we could not get compliance with random assignment procedures. We cannot use statistical techniques to get approximate answers because of the dissimilarity in populations served by therapeutic communities and by maintenance programs. Drug use patterns as well as age, sex, and ethnicity all appear to discriminate those who use therapeutic communities from those who use methadone maintenance programs. There would seem to be no question that methadone maintenance programs are superior in terms of retention in treatment. The success of retention in methadone maintenance programs is diminishing in recent years, but is still higher than that associated with therapeutic communities. Realistically, I cannot see a design which would permit a scientific assessment of methadone maintenance and therapeutic communities because of the compliance question. The comparison is false, in any event, because addicts who use therapeutic communities are different from those who use methadone programs.

There is no basic problem with studying effects of variation of therapeutic community modalities. Sells describes three basic types. I would place such studies high on the evaluation agenda for the next decade. Dr. Bale at Stanford has conducted a study along these lines which should be replicated (Bale et al. 1980).

The foregoing discussion is predicated on an assumption which is implicit but which is highly significant. Our focus is on the individual addict. Sells' typology, for example, does not describe treatment programs with and without outreach. Stated differently, our focus has not been a public health focus. Can treatment programs have such a focus? We have experience in Illinois suggesting that they can, and indeed for maximum effectiveness, should. But the issue requires much more study on a broad scale before we can conclude anything. Again, the relevance in this context is that NIDA's research agenda for the future should give systematic consideration to the public health perspective in drug treatment. Epidemiology and treatment can be combined as Dr. Hughes (1977) has pointed out.

Having discussed variations in methadone maintenance programs and in therapeutic communities briefly, I would like to turn to discuss detoxification programs. Two important types of detoxification require discussion: detoxification only, in Sells' terminology, and detoxification followed by aftercare sometimes involving the use of a narcotic blocking agent such as naltrexone. The data on this latter option suggest that compliance is low but that it is a useful option for some addicts. Detoxification only does not appear to have benefits beyond a brief period of reduced level of dependence and some lessening of the need to engage in criminal activity. But there does appear to be variance in detoxification programs attributed to such factors as expectations regarding the experience of withdrawal and rate of withdrawal. Further studies of expectation and rate of withdrawal are needed. The studies we have need replication, and we need to carry out basic research on the biology of withdrawal. In my opinion, a high priority should be put in basic research on both acute withdrawal states and perhaps most importantly on chronic withdrawal states, i.e., the protracted abstinence syndrome.

Adequate resources would enable us to study a basic question in maintenance programs, namely, whether the provision of a counselor, job preparation, admission, group seminars, etc., contributes to success beyond what we would get with the simple provision of methadone. Our attempt in Illinois to study this question failed because of a lack of resources. Future studies should settle this question. Again, this is the type of study which needs micro-level and macro-level attention. Macro-level attention would mean multiple sites to control for community and staff variables.

The role of psychotherapy as distinct from counseling in drug treatment represents a question of major importance (LaRosa et al. 1974; Longwell and Miller 1978; Willett 1973). If, as the data mentioned by Dr. Woody indicate, psychotherapy can improve success, then the form of programs has to change with more training of staff to carry out psychotherapy. This question, like the others I have discussed above, is difficult to describe without considering patient compliance. Many patients clearly do not want psychotherapy but still may change behavior in desirable directions. The studies required appear to be self-evident and should have a high priority for NIDA's research agenda.

Finally, I think we need to consider whether or not there are new treatments which should be tried on a national scale. At this time, I don't see any which merit national trial; acupuncture, meditation, etc., do not have a respectable data base. The momentum at present seems to be away from opioids and toward multiple drugs. The implication is that our national treatment effort has to be aimed at a younger, more geographically mobile population whose needs appear to be short-term contacts with the treatment system. Epidemiologic studies both on a macro- and a micro-"ethnographic" level are needed to help us change the national system so that it fits the kind of drug problems we are facing. The logic of the data we have gathered during the past decade on drug abuse trends, together with the data we have on utilization of our current system, suggests that we should emphasize detoxification programs. They seem to be wanted, and I think we should view them as gateways to the longer-term treatments. I am not suggesting that we abandon maintenance programs or therapeutic communities, but we should increase the number and quality of our detoxification programs and create a better balance between detoxification, methadone maintenance, and therapeutic communities.

It is important that we view treatment as heterogeneous because addicts are heterogeneous. The multimodality concept should not be neglected. Detoxification, methadone maintenance, and therapeutic communities should supplement one another and not compete with one another. NIDA's research agenda should keep this in mind.

I would summarize my critique by suggesting that NIDA create an explicit research agenda which is responsive to a number of needs and trends in the field: first, to consider trends toward the use of multiple drugs including alcohol (these have implications I have discussed above); second, the need for epidemiologic and public health perspectives to determine what is studied and how it is studied; third, to study macro- and micro-levels of phenomena; and last, to create a research agenda which will unify the field by recognizing that our current treatment methods are not antithetical but are complementary.

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DISCUSSION SUMMARY

Fred Altman, Ph.D., and Sidney H. Schnoll, M.D.

Methadone maintenance includes not only the administration of methadone but also the supportive and rehabilitative services required by the patient. For some patients, it is necessary to provide these services directly as part of treatment. For others, direct services other than methadone are not required; it appears that adequate support is obtained through family, friends, jobs, etc. There was general agreement among the participants that methadone maintenance is an effective treatment for opiate addiction. The studies by the Institute for Behavioral Research at Texas Christian University were often mentioned in this regard.

The necessity of replicating Dr. Woody's findings on the effectiveness of psychotherapy for those with psychopathology was noted. There was little discussion of interventions aimed at other patient problems (e.g., vocational counseling or supported work for the unemployed, family counseling for individuals with family problems, contact with patients who leave against medical advice).

There was general agreement that outcome was affected by the patient's relationship to something in the program in addition to methadone, but whether it was the specific counselor, daily visits for methadone, special programs (educational, vocational, or psychotherapy), or legal interventions remains to be determined.

The importance of detoxification as a treatment approach or as part of long-term treatment was presented. Although there are no data to support the long-term efficacy of detoxification alone, this treatment is effective in reducing drug use temporarily and there is demand for such services. Consequently, some of the participants felt strongly that detoxification programing should be improved to make it a more effective entre to other forms of treatment. There was doubt expressed regarding the appropriateness of the 21-day limit placed on the initial detoxification process. The content of the discussion is comparable to the more detailed discussion found in part I, Chapter 5.

Staff attitude was discussed as an important factor in outcome. There are staff who work in methadone maintenance programs who do not believe in the effectiveness of methadone or understand its appropriate role. This may lead to patients being placed on too low a dose or being withdrawn from methadone prematurely. It also appears to result in the patients adopting a negative attitude toward methadone with consequent loss of self-esteem and requests for premature detoxification. There was some discussion that the use of the term "client" as opposed to "patient" reflected a negative attitude toward these individuals.

Although it was agreed that we have to know much more about what works in treatment, there was disagreement about the type of research which would most likely provide the knowledge. Some participants felt the large-scale studies of treatment effectiveness which have been going on for several years should be continued; i.e., it was felt that treatment factors affecting outcome could be discovered by studying the differential outcome from various clinics and then investigating the characteristics of those clinics and the patients they serve.

Other participants felt that as much as could be learned from the macro-studies has already been learned, and it was now time to investigate how individual services within clinics affect outcome. The debate of macro- vs micro-studies continued as a major theme of the discussion throughout this meeting. Despite this prevailing theme, there was little agreement of what specific treatment characteristics or services would be the most important to study.

CHAPTER 3. METHADONE TREATMENT: A REVIEW OF THE RESEARCH FINDINGS

Sharon M. Hall

This paper reviews the literature on services and treatment structure as they relate to methadone maintenance treatment outcome. The literature is reviewed in two sections. The first examines the efficacy of treatment services other than provision of methadone, including psychotherapy and vocational rehabilitation. The second examines the larger treatment environment, including program structure, staff training and experience, and attitudes.

The questions asked in intervention research in drug treatment are straightforward: for example, does family therapy decrease illicit drug use? The sophistication of the methodology used to answer such questions is generally the key to the confidence attached to the answer. In this review, factors to be considered in evaluating studies are research design (especially the internal validity of the design), outcome measures, control of attrition, sample size, and length of follow-up period.

Research Design

The research reviewed in this chapter can be grouped into three design categories, which are described in order of increasing internal validity. Internal validity is the extent to which we can say an effect occurred and can be attributed to a particular treatment. My bias, shared with Shontz (1965), Campbell and Stanley (1963), Paul (1969), and Mahoney (1978), is that the confidence with which one can draw cause-effect conclusions about treatments increases as one moves from case studies to correlational ones to true experimental designs, if all studies are equally well implemented for their type. In intervention research, the handling of nonspecific attentional factors and therapist and client characteristics also contribute to the internal validity of the research design.

Case Studies. At the lowest level is the uncontrolled individual or multiple case study. Except for the rare case study which disproves a theory, even the most carefully done case study can only suggest hypotheses. Confounding variables whose effects cannot be known include the action of environmental, psychological, and biological factors associated with the passage of time, therapist and client characteristics, and nonspecific or attention-placebo effects (Paul 1969). Also, if the case study reports results for a single subject, the results may well be unique to that subject. Aggregate data describing a treatment program are at the case study level.

Correlational Designs. At the next level are correlational designs (Shontz 1965), distinguished by identification of relevant variables to be measured, rather than systematically produced differences between variables. The crucial difference between correlational designs and true experimental designs is that in correlational research the comparison conditions are preexisting. Treatments given to these comparison conditions are only measured, not manipulated. A primary weakness of the correlational design is that differences observed between conditions may reflect the effects of unknown (or known) confounding variables. Statistical methods, such as analysis of covariance, can artificially remove the effects of such variables. However, the researcher (and the reader) can never be sure that the variable removed was in fact the cause of the confounding, and not a variable correlated with the causative one. Yet in many instances correlational designs are of great value, for they permit examination of interventions in situations where true experiments are impossible, for example, where clinical concerns prohibit random assignment to treatment conditions, or where answers to interesting questions can be found only in retrospective analyses.

Experimental Designs. One can be most certain that a particular treatment produces a particular effect when that treatment is evaluated in one of the variants of the "true experiment." The first variant is the within-subject design in which comparisons are made within the same subject(s) across differing conditions. This design can control for the effects of factors other than the treatments themselves and allows the assigning of cause-effect relationships. It has been widely used in evaluating the effects of contingency management systems. Theoretically, the design can test therapist and

attention-placebo effects, if these two variables are manipulated. This has not been the case in any study I could find in methadone treatment research, although relevant examples exist in the psychotherapy literature (Leitenberg 1976). Small numbers of subjects are almost always used. Therefore, it is usually impossible to determine how subject characteristics interact with treatments.

A second, more common variate of the experimental design is the between-subject comparison study. Subjects are randomly assigned to conditions, and one group of subjects receives a particular treatment while the other does not. It is possible to examine the effects of differences in therapist and client characteristics on the treatment interventions. A treatment/no-treatment design does not control for the nonspecific effects of simply being in treatment, however.

Other experimental treatment designs are variants and expansions of the basic two-group design. In many instances in drug treatment, no treatment controls are considered unethical, or are impractical. Thus one or more comparisons can be made with other treatments, often with differing amounts of contact (e.g., Rounsaville et al. 1982).

Variants of the Experimental Design. The following important parameters can affect experimental design and can contribute to outcome.

Nonspecific controls. More methodologically sophisticated designs use a nonspecific control group, which provides a treatment equal in time, therapeutic contact, credibility, and client expectations, but does not have the specific components hypothesized to cause changes. It allows an evaluation of the active components of the experimental intervention versus the nonspecific effects resulting from simply being in treatment. I could find only one example of study condition approaching a nonspecific control in the methadone treatment literature (Stanton et al. 1980).

Therapist effects. The least desirable design is one in which a single therapist administers all treatments, thus confounding therapist effects with the specific effects of treatments. There have been two common solutions to this problem. The first is to cross therapists with

treatments, so that all therapists administer all treatments. Thus, any effects will not be specific to one therapist, who may be extraordinarily skilled in a particular therapy, or so convinced of its efficacy that its superiority is practically assured. A danger in crossing therapists with treatments is that all therapists will be biased in the same direction, and that differences between conditions will reflect these biases. The usual safeguard against this is to prepare therapist manuals which describe in detail the behaviors to be completed by the therapists, to monitor their behavior to ensure that the treatments are provided in such a way to minimize bias, and to query subjects about their perceived credibility and efficacy. A second solution has been to select different therapists expert in the different treatments provided (e.g., Woody 1981) and assume that each set of therapists will be biased toward the particular treatment they offer. Potential confounding variables include differential credibility of therapists (e.g., psychiatrists vs exaddict counselors) and the difficulty of equating "expertness" in widely different therapies.

Neither of these two solutions is ideal. However, the ideal is not attainable, for it would involve a treatment X therapist factorial design in which therapists, equally competent in the various therapies, and equally persuasive, would have no opinion or expectation of the effectiveness of the therapies.

Client characteristics. A treatment which is effective for clients with a particular set of characteristics may be ineffective for other clients. Methadone maintenance clients have a broad range of behavioral and psychological characteristics (cf. Rounsaville et al. 1982). Frequently, a first step is to identify clients who do well in a particular treatment. For example, in the Job Seeker's Workshop studies (Hall et al. 1981b) we found that subjects who had not been employed in the last 5 years were not helped by the intervention. However, this finding may not be specific to that intervention, but may hold for any vocational rehabilitation intervention involving methadone maintenance clients. The most sophisticated designs are those which match client characteristics to differential success in particular treatments (e.g., Woody 1981).

Outcome Measures

Seven categories of outcome are important in methadone maintenance. These are: 1) drug abuse; 2) illegal activities; 3) employment; 4) program retention; 5) social functioning; 6) intrapersonal functioning; and 7) physical health and longevity. Within the treatment community, there is considerable debate over the operationalization of some of these goals, and their priorities. For example, should methadone patients be expected to refrain from use of all illicit drugs, including marijuana and cocaine, or should programs direct their efforts primarily to the eradication of heroin use? Different investigators put differing emphasis on these outcome categories as a function of their own treatment philosophy, the goals of the service or program evaluated, and the availability of data.

My bias is that three criteria must be kept in mind when evaluating the adequacy of measurement. The first is the reliability of the information obtained. For a variety of reasons, including conscious and unconscious distortion and lack of awareness, it is generally assumed that simple self-report data are less desirable than objectively verified information. This is especially true when the response has a cost, such as reports of illicit drug use. In some instances, self-report may be inaccurate simply because the respondent does not have the vocabulary or observational skills to assess his or her own behavior. On the other hand, there are some data indicating that if there are no incentives to falsify a report, especially of simple behaviors, or if respondents believe their veracity is being monitored, self-report is reliable (Hall 1972; Amsel et al. 1976; Maisto et al. 1979). Thus, judgment about reliability is often specific to each variable. Fortunately, in most studies in drug treatment, objective verification of self-report is provided by treatment system data. Second, given the multiple criteria of success, and the wide-ranging effects of drug abuse on the individual's life, studies employing outcome measures assessing multiple areas are superior to those which focus on a single area. Finally, the degree of relationship between measures and the goals of the intervention should be a close one. For example, changes on scales of personality characteristics may be of theoretical interest, or contribute to process analyses, but they are not appropriate as primary outcome measures in most studies of services in methadone treatment. The assumption which underlies use of such measures, that changes in personality characteristics mediate changes in drug use, is an unproven one.

Treatment Attrition

Attrition affects treatment research prior to the start of a study, during treatment, and during follow-up.

Only a certain percentage of potential subjects recruited will enter a study. This percentage reflects both the attractiveness of the experiment (e.g., subject payment) and the attractiveness of the treatment. Attrition after treatment assignment is usually linked to the treatment.

In drug treatment research, a frequent threat to the design is differential attrition between treated and control groups which destroy their equivalence. In such cases, the effects of the treatment on both the attenuated sample and the entire experimental condition must be considered. This is not an entirely satisfactory solution, since dropouts may never have received the experimental treatment, or received little of it. The partial sample of treatment completers is self-selected, and probably more motivated to change.

Subjects lost to follow-up can reflect either deficiencies in the investigator's methodology or the results of treatment. It is often assumed that subjects lost to follow-up are those with the worse outcome, and these subjects are frequently placed in the worst outcome categories for purposes of analyses. Thus, differences in follow-up rates between conditions may reflect differences in long-term treatment outcome.

Sample Size

A common error in early intervention research was to use too small a subject sample; even if differences actually occurred, sample sizes were too small to detect them. For over a decade, however, methods to plan sample size have been widely available (Cohen 1969). Recent research is more adequate in this respect. Sample size can be a special problem when high rates of attrition occur, and the final sample is even smaller than originally planned.

Length of Follow-up

Relapse is a common problem in all the addictions (Hunt et al. 1971). Because of this, adequate follow-up periods are necessary to demonstrate the clinical usefulness of a

technique. Length of optimal follow-up varies with the problem under study, since follow-up should continue until relapse rates reach an asymptote. There is some suggestion that relapse in the addictions is greatest during the first 6 to 12 months following the termination of treatment, with little increment occurring after this time (Hunt et al. 1971), although exceptions do occur (e.g., Stimmel et al. 1977). Scientifically, the longer the follow-up the better. However, cost and logistics often preclude follow-ups longer than 1 year.

THE EFFICACY OF PSYCHOSOCIAL INTERVENTIONS IN METHADONE TREATMENT

Psychotherapy

Three variants of psychotherapy have been studied with sufficient frequency in methadone treatment to allow review. These are family therapy, psychodynamic psychotherapy, and behavioral psychotherapies.

Family Therapy. The hallmark of family therapy schools is a focus on the identified client as part of a system. Symptoms, such as drug abuse, are seen as ways of focusing attention away from events which might destroy the equilibrium of the system. The members of the system strive to maintain equilibrium within it. Thus long-term positive change is impossible unless the system itself is modified. The most frequently cited family approaches are the systems methods of Jay Haley (Haley 1971), and the more psychodynamic focus of Minuchin (1974) and Boszormenyi-Nagy (Boszormenyi-Nagy and Spark 1973).

The family is a focus within many drug treatment clinics. Coleman (1977) surveyed 3,335 agencies identified by the 1976 National Drug Abuse Treatment Utilization Survey (NDATUS). Of the 1,986 (60 percent) agencies responding, 1,846, or 93 percent, reported providing some services to families of drug abusers. If it is assumed that all nonresponding clinics provided no family services, these data still indicate that over half (55.4 percent) of the clinics in the NDATUS sample provided some form of family service. Methadone maintenance clinics were 18.5 percent of the sample. They most frequently offered couples therapy for the client and spouse, followed closely by family therapy including the client and the family of origin.

Family "service" is not equivalent to family "therapy." Still, these data do indicate an interest in, and focus on, the family.

Despite this level of interest, and despite a sizable literature on family therapy, few data on family services in methadone maintenance exist. A "family-oriented" methadone maintenance program for pregnant addicts and their addict spouses at SUNY Downstate Medical Center in Brooklyn has been described in several publications (Silver et al. 1975; Arnon et al. 1978; Panepinto et al. 1977). This clinic treated young, primarily black clients, most of whom were involved in a stable relationship. Treatment included family sessions, instruction in child care, and other supportive services aimed primarily at the women clients. Their partners were often in treatment at the clinic also. Of the 147 clients initially treated, 40 percent were reported to achieve and maintain drug free status, 6 percent were admitted drug free, 10 percent were detoxifying, and the remaining 44 percent were on methadone doses of less than 60 mg. The clinic encouraged detoxification when appropriate, and reported success. Of 70 clients who attempted detoxification, 62.9 percent remained drug free and in contact with the program for a mean of 11.5 months. An additional 24.2 percent of those attempting detoxification continued in maintenance and were stabilized at lower doses of methadone. These outcomes are relatively promising. However, due to the case study nature of the report, nothing can be concluded about the causal link between the outcomes and the treatment program.

A small-scale controlled study of family therapy in methadone maintenance treatment was described in a brief report by Panio (1980). Therapy was based on the theories of Kramer (1968) and Minuchin (1974). Subjects were 30 ex-addicts who were accepted into treatment only if their families agreed to participate. They were randomly assigned to family treatment, individual counseling, or psychotherapeutic treatment. The single therapist for both groups treated was an expert in family therapy. Subjects were assessed at the end of the 8-week treatment. The 19 subjects who completed the 6-month methadone treatment program were assessed at 6 months. The author reported that the family therapy group had more drug free days, more clients completely detoxified from methadone, a lower mean dose of methadone for those still on the program, the highest percentage of clients employed or in school, and the highest percentage of program completors at 8 weeks

posttreatment, and maintained differences at 6-month follow-up. However, from the data presented, it appears unlikely most of these differences would approach statistical significance. For example, the number of subjects employed or in school at 8 weeks are 5/9 (56 percent), 5/11 (45 percent) and 4/10 (40 percent) for family therapy, individual counseling, and control conditions, respectively, a difference which is not statistically significant. This lack of differences in part reflects sample sizes so small that only very large differences would be detected. Lack of statistical significance coupled with the use of a single therapist who appeared to have a specific bias toward family therapy, and expertise in it, makes it impossible to draw any conclusions from this report.

An evaluation of family therapy was completed by Stanton and his associates (Stanton et al. 1980). To be eligible for the study, male applicants for methadone maintenance had to meet a restrictive set of criteria, including regular contact with parents or surrogates and both parents living together in same household. It is surprising that over 25 percent (215/836) of the clients screened met these criteria. Eligible subjects were assigned to family treatment, if an opening existed. If not, they were assigned to a standard treatment control (N=53). Family treatment subjects were randomly assigned to either paid family therapy (N=21), unpaid family therapy (N=25), or paid family movie treatment (N=19). Therapy was modeled after the structural family therapy of Minuchin (1974) and Haley (1971). This technique involves active therapist intervention with defined, symptom oriented goals. In the two paid conditions, family members were paid for attendance and for the provision of drug free urine specimens by the client. All conditions met once per week for 10 weeks. The movie treatment served as a control for payment and for family attendance at clinic sessions. Mean number of sessions attended were 9.4, 5.8, and 8.7 for paid therapy, unpaid therapy, and paid movie, respectively. Thus, payment significantly increased attendance.

Interview data obtained for two 6-month blocks following family treatment indicated somewhat different patterns of outcome for these blocks. In the initial 6 months, the most important finding was that both the paid and unpaid family condition had more drug free days in most categories of drug use than the movie group or the nonfamily group. Differences were stronger for the paid family than for the unpaid family group. No differences in alcohol

use, or in days spent working or in school were found. In the second 6 months, differences between the conditions were less. The data indicated maintenance of therapeutic gains for the paid family group, while the other two groups continued to improve gradually so that differences between the conditions were less often significant during the second 6 months. The authors explain the superiority of the paid family therapy condition as a result of increased attendance at therapy sessions, which enabled the therapy to "take effect" more readily. This study was characterized by both a high pretreatment dropout rate (30 percent (39/131) of the subjects assigned to family treatment, and 37 percent (31/84) of the subjects assigned to nonfamily), and a substantial rate of refusal to participate among family therapy assignees (21 percent (27/131)). However, careful analyses of descriptive characteristics and outcome for early dropouts and treatment rejectors failed to indicate any compelling evidence that the legitimacy of the comparisons was compromised by preexisting differences between treatment conditions. It is also plausible that the nonrandom nature of the nonfamily control could have introduced some unknown bias. However, if this occurred, it was not evident to the authors, or to me. Attrition at follow-up was moderate. At 6 months, 10.9 percent of the cases were excluded. At 1 year, as many as 17 percent of the cases were missing on some variables. Attrition was not differentially distributed across treatments.

This study provides evidence that family therapy may be of value in the treatment of methadone maintained men. Replication of this work in different samples, especially ones including female clients, could be of value. Family dynamics might be quite different for females. Stanton et al. (1980) document the extensive therapist involvement needed to recruit family members into therapy. Combining contingencies with active therapy appears to be one way to increase that engagement. While this study used payment, many clinic-controlled contingencies are more cost effective, and might be used in a similar manner.

The paid family movie condition is an interesting innovation. However, it would not appear equal in credibility or expectations of success to the family treatment condition. Also, since it was conducted by a drug counselor, rather than a family therapist, therapist status and expectations about change may have played a role in determining outcome. Thus, while the paid family movie condition controls for amount of contact, and for use

of contingencies without other therapeutic intervention, therapist variables are again confounded with treatment, and the effects of differences in therapeutic attention and client expectations are unknown.

To summarize the family treatment literature, treatment clinic staff find family therapy attractive, and at least one adequately designed study suggests it may be of value in reducing illicit drug use. Only one form of family service has been evaluated: conjoint family with the family of origin. A surprisingly large proportion of methadone clients may be eligible for such treatment. Other family therapies have not been studied. Since methadone clinics are more likely to offer marital therapy than conjoint family therapy, the lack of a controlled study of the effectiveness of marital therapy is unfortunate.

Methodologically, the family therapy area is weak, with only the study by Stanton et al. using a design, subject sample, length of follow-up, and verifiable measures of drug use which allow reasonable if tentative conclusions about the efficacy of the therapies provided in the study.

Psychodynamic Psychotherapy. Psychodynamic therapies emphasize the need to uncover unverbalized emotions and conflicts which impair the client's functioning. The exact role of the therapist may vary, but it is assumed that the therapeutic relationship in itself is central in causing change, through the analysis of transference and countertransference issues.

In some reports, psychotherapy or "psychotherapeutic counseling" is evaluated in a mix with other ancillary services, such as vocational rehabilitation services, or legal and dental care, and its effects are impossible to determine (Senay et al. 1973).

The earliest study addressing the use of psychotherapy in methadone was that of Ramer et al. (1971). These investigators attempted to complete a controlled study of services. Half the sample was to receive methadone plus group and individual psychotherapy, crisis intervention, vocational guidance, and "other treatment modalities deemed advisable by the staff." The remaining subjects were to receive methadone only. The original design was discarded, however, when it became clear that many clients in the group receiving only methadone showed a need

for services. All clients were given access to services, and use recorded. While 79 percent of the clients used crisis intervention, only 23 percent used individual psychotherapy, 30 percent used group psychotherapy, and 16 percent used conjoint psychotherapy at some point in treatment. Subjects who used individual psychotherapy appeared to do poorly in the program. However, this result may have been confounded with a generally higher rate of use of services by clients with greater psychopathology, who would be expected to do more poorly in treatment. Details about the kind of psychotherapy offered were not given.

Davidson (1977), Khantzian et al. (1974), and Wurmser (1972) have described the possible psychodynamics of the methadone maintenance client. Wurmser also presented data on 14 methadone clients seen in intensive psychodynamic psychotherapy. Therapy was based in part on the assumption that drug abuse and serious character disorders were always correlated. Wurmser described the prototypical addict as characterized by feelings of rage, shame, and rejection, and driven by underlying conflicts of omnipotence and unrealistic expectations of others. Heroin use is seen as cure for the disillusionment, hurt, and loneliness which stem from these psychogenic states. The outcome of treatment was not favorable. Of these 14 clients, "ten had to be discontinued from methadone treatment during that period, either for financial or administrative or for internal (psychogenic) reasons, and the other four who are still or again on methadone maintenance could not be continued in psychotherapy." These clients were largely white and middle-class. Black and lower-class clients offered the opportunity to participate refused.

Willett (1973) compared analytically oriented group psychotherapy with a T-group and a standard treatment control. Each group was led by a different (male) therapist. Subjects were assessed preand posttreatment on the Interpersonal Checklist (Leary 1957). Of the original 30 subjects, only 18 remained in the 8-week treatment by termination. At the end of treatment, the analytic group showed the largest number of changes on the Interpersonal Checklist, and the only significant prepost change, an increase in the Rebellious-Distrustful sector. However, the author hypothesized that this change may have been due to the unique characteristics of the therapist in this condition. The extremely small subject sample, coupled with the high attrition rate, may have resulted in

inadequate statistical power to detect other differences, if they existed. Also, from the description of the psychodynamic group, it is unclear that the therapy provided would be considered psychodynamic by most standards. Instead, the focus of the group was "the past and how 'it' used to be." Finally, the outcome measure seems of little relevance to methadone treatment.

Two recently completed studies promise to provide more information on the efficacy of psychodynamic psychotherapy in methadone treatment. An ongoing study evaluating supportive expressive therapy (a psychodynamic therapy), cognitive behavior therapy, and drug counseling is described elsewhere in this volume by Dr. Woody. Briefly, on entrance into treatment, methadone clients were randomly assigned to one of the three treatment conditions. In supportive expressive therapy, clients identified and worked through important relationship themes. Clients in the two psychotherapy conditions were seen by professional therapists, and also received standard drug counseling from a paraprofessional counselor. In the control condition, only drug counseling was provided. Clients could continue in treatment with their therapist for up to 6 months. Clients were assessed on the Addiction Severity Index (McLellan et al. 1980), a multiscale index which taps medical, legal, drug and alcohol abuse, employment, family, and psychiatric problem severity, on urine test results and methadone dose, and on licit prescription drug use.

The preliminary analyses of outcome for the first 62 clients indicate that on several measures, both of the psychotherapies are superior to standard drug counseling but only for clients with high initial levels of psychopathology.

It is possible the superior outcome for clients treated with psychodynamic and cognitive behavior therapy in this study reflects the greater prestige of the professional therapists who provided it, although the data from other studies do not entirely support this interpretation. Several studies have shown methadone clients value paraprofessional counselors at least as much as they do "professional" ones (Ball et al. 1974; LoSciuto et al. 1979a). Also, the preliminary finding that both forms of psychotherapy were more effective for clients with high levels of psychopathology suggests that psychogenic changes rather than therapist status variables were important. It should also be noted that clients in the

psychotherapy conditions received more hours of contact than did clients in the drug counseling condition. This attentional variable may have affected outcome.

Another preliminary report on this study provides data on client attrition (Woody et al. 1979). About one-third of the eligible clients did not complete the three preliminary meetings with the therapist necessary to be accepted into the study. These preliminary analyses also indicated a somewhat greater involvement in psychodynamic psychotherapy when compared to the behavior therapy. While 62 percent of the former were judged "moderately or heavily engaged in therapy" (a judgment based on number of sessions attended), only 40 percent of the cognitive behavior therapy clients were judged to be at this level of engagement. Clients in psychodynamic psychotherapy attended a mean of 14 sessions; clients in cognitive behavior therapy attended a mean of 10 sessions. Final data on attrition in the study are not available.

The second study is a recently completed evaluation of Short-Term Interpersonal Psychotherapy for methadone clients who showed evidence of psychiatric disorders (Rounsaville et al. 1983). Short-term interpersonal therapy assumes psychiatric disorders reflect disturbances in relationships, and that improvement in interpersonal functioning may lead to both symptomatic improvement and relapse prevention. Subjects were 72 clients who had been diagnosed as showing a current psychiatric disorder such as anxiety or depression. Clients doing poorly in treatment or having significant psychopathology were especially encouraged to attend. Subjects were randomly assigned to either the interpersonal psychotherapy or to a control condition. In the psychotherapy condition, subjects received 1 hour of individual therapy per week with a professional therapist. The control condition did not receive individual psychotherapy, but did meet once per month for 20 minutes with a psychiatrist who reviewed symptoms and social functioning. Both conditions received the standard 90-minute group therapy provided all clients, and access to all clinic services. Treatment was available for as long as 6 months. Outcome measures included treatment attrition, number of urines positive for illegal drugs, arrests, measures of depression, psychiatric symptomatology, personal and social functioning, and attainment of individual goals. Attrition was high in both conditions; 38 percent of the subjects completed the psychotherapy condition and 54 percent completed the control condition.

Subjects were difficult to recruit into treatment. The 72 subjects recruited over the 3-year course of study were less than 5 percent of the over 300 clients maintained on methadone at a given time by this program. Also, the results indicated few differences between the two groups. The authors discussed several factors which might have obscured differences between conditions. These were the large amount of counseling provided all subjects, the selection of only subjects with psychopathology to participate, and the restriction that subjects could be recruited into the study only after having been in methadone treatment for 6 weeks, when motivation to change may have been less than earlier in treatment. I agree with them, and add two additional factors. The first is that the therapy offered in the 90-minute group sessions could have provided conflicting therapeutic directives to those of the individual sessions, thus diminishing the effect of the therapy. The second is that by encouraging clients who were not doing well in methadone treatment to enter psychotherapy, the most noncompliant clients may have been included in the study. This would explain the extremely high dropout rates as well as the failure to find differences between treatment conditions.

There are not enough data to come to a conclusion concerning the value of psychodynamic therapy in treating methadone-maintained clients. Only the two most recent studies are sufficiently well designed that efficacy can be evaluated, and their preliminary findings are in conflict. With the notable exception of Woody et al., the most consistent findings in the case and experimental studies on psychodynamic psychotherapy have been the relative difficulty of engaging methadone treatment clients in such treatment, as well as the difficulty of holding them in treatment once begun. Several factors probably contributed to this finding. Most psychodynamic psychotherapy is based on the assumption that the client has psychogenic conflicts and problems which impair living. While methadone staff believe this to be true of their clients, the patients themselves do not view themselves as having psychological problems (Ball et al. 1974). Also, methadone clients are a diverse group. A specialized modality, such as psychotherapy, should not be expected to be of value to all clients, or even a majority of them. Further, most addicts are members of working and lower-class populations, who are less amenable to psychotherapy of any form than members of the middle class.

In methodology, the research on psychodynamic psychotherapy is at a stage similar to family therapy research. After early case studies, and attempts at controlled studies which were not completed, outcome methodology has developed to the point that meaningful questions about outcome can be asked. However, many questions have not been addressed. The issue of attention controls has yet to be considered. Also, attrition is severe enough to be a methodological problem as well as a treatment issue. One wonders what the results would have been had the investigators been able to contain attrition through payment or other means, and thus actually exposed greater proportions of the subject sample to it. Finally, the effects due to therapist and therapeutic attention have not been fully controlled.

Behavioral Therapies. All behavior therapy models assume that maladaptive behaviors are learned, and with proper, direct relearning experiences, such as skill training, relaxation therapy, or aversive conditioning, more adaptive behaviors can be learned. The causal variable may be internal, as when anxiety interferes with detoxification, but it is always assumed to be amenable to direct retraining.

In conjunction with methadone maintenance treatment, the most frequently applied behavioral technique has been relaxation training or its technologically more sophisticated variant, biofeedback. These techniques have been used primarily to reduce clients' anxiety. The assumption underlying use of the techniques is that the tension reduction effected by drug use is a powerful reward for drug use. An alternate method of tension reduction should decrease use. Detoxification anxiety has been the target in several studies. Such anxiety has been conceptualized as a phobic reaction to the stimuli associated with detoxification, including both internal stimuli and the interpersonal consequences of detoxification (Hall 1979, 1982; Milby et al. 1980).

The literature on relaxation training provides a sobering lesson in the difference in the cause-effect relationship which is assumed in case studies and other uncontrolled reports, and that which is revealed when well controlled outcome experimentation is used to study the usefulness of a technique.

Goldberg et al. (1976) trained four patients to control alpha activity over a 5-week, 10-session training period. Descriptive information, not data, is presented. Only moderate alpha control was achieved, but clients reported increased relaxation and a heightened sense of personal control. All reported less use of drugs and two expressed a desire to detoxify. Counselors reported positive changes in self-confidence and openness by participating clients. Program urine screens showed a reduction in "dirty urines." Shapiro and Zifferblatt (1976) reported successful detoxification of two clients after training in imaginal rehearsal of adaptive behaviors, focused breathing, and self-instructions. Clients were also instructed in meditation. Both clients detoxified from drugs and remained drug free at 2-year follow-ups. Shapiro and Zifferblatt hypothesized that the relaxation induced by meditation may have been part of the effectiveness of this treatment program. Positive results were also reported by Brinkman (1978). He treated 22 clients with electromyogram biofeedback ancillary to detoxification. Clients reported increased relaxation, fewer sleep disturbances, and increased insight. Detoxification data were reported on six clients. Two detoxified completely, and an additional two continued slow detoxification.

Perhaps the most impressive outcome of all the case studies were clients' self-report on the relaxation experience. Typical comments, consistent across studies, were that the relaxed state was similar to an opioid high, that it made the clients feel clear-headed and in control of their lives, and that it decreased the urge to use drugs.

The findings of two controlled studies contrast sharply to these case reports. Khatami et al. (1978) randomly assigned clients to biofeedback (N=13) or a standard treatment control (N=7). Biofeedback clients received 15 sessions in a 3-week period. Both groups improved over the course of treatment. Biofeedback clients showed greater improvement on the measure of anxiety than did controls. Treatment completers (N=7) improved significantly on both self-reported and psychiatrist-rated depression, and were significantly better than controls on percentage of "clean" urines and attainment of drug free status. This was not the case when all experimental subjects were compared with controls. Differences were not significant.

We have completed a larger-scale, controlled study of relaxation training as an ancillary to methadone detoxification (Hall et al., 1982). Fifty-three subjects were randomly assigned to either a Relaxation Information condition, or to a standard treatment control. Relaxation Information clients received a 5-week course of treatment in which they were taught to redefine withdrawal symptoms, and were given training in both cognitive relaxation training (Beary et al. 1974) and in classical progressive muscle relaxation (Jacobsen 1934). Clients were also taught to recognize cues in situations related to anxiety and to practice the relaxation response when confronted with these cues. Two experienced therapists each led half of the treatment groups. Clients were assessed at weeks 0, 5, 12, 24, and 52. Assessments included measures of general and detoxification-specific anxiety, mood state, withdrawal symptomatology, and self-reported alcohol and drug use. Methadone dose and urine test results were collected throughout the 1-year follow-up period. Seventeen of the 27 experimental clients completed treatment. Ninety-one percent of all subjects were successfully followed. Preliminary data analysis, using all subjects entering into treatment, indicated little difference between the experimental and control subjects in methadone dose reduction or complete detoxification over the year. Experimental subjects reported less alcohol use and fewer withdrawal symptoms immediately following treatment, but these differences were no longer evident at later follow-up periods. No differences in other psychometric measures were noted, including anxiety. Five of the control subjects received disciplinary discharges. None of the experimentals did so. However, this may simply reflect staff unwillingness to refuse treatment to subjects who are involved in extra therapeutic activities at the clinic. Our preliminary conclusions are that the few positive differences between experimental and control conditions can be explained in terms of increased therapeutic attention, and are probably not due to the technique. As in the case studies, patients reported use of the technique lowered tension levels, and compared the relaxation experience to an opioid high.

In summary, relaxation training and its variant, biofeedback, are not effective treatments for methadone maintenance clients, even though clients report increased relaxation and enjoy use of the technique. The technique does not appear to change drug use or affect other objective variables. Data on mood state changes are conflicting. Khatami et al. found some differences for treatment

completers, but such differences can most simply be explained by motivation to change among this self-selected subsample.

There are four studies in the literature which used other types of behavioral psychotherapy with methadone maintenance clients. Two of these (Snowden and Rosenbaum 1975; Hirt and Greenfield 1979) measured only short-term behavior change. Snowden and Rosenbaum assigned 42 heroin abusing methadone maintenance clients high and low in internal control (the extent to which one believes one's actions influence outcome) to either 1) relaxation and discussion; 2) "internally oriented" covert sensitization; or 3) "externally oriented" covert sensitization in a 2 (locus of control) by 3 (treatment condition) experimental design. In covert sensitization, an undesired behavior (heroin use) is paired with imaginal aversive consequences. In this study, the imaginal consequences were either internal, e.g., guilt, or external, e.g., physical violence. At the end of five treatment sessions, a significant treatment by locus of control interaction was found in urinanalysis results. Internal subjects in the internal sensitization group had a mean of only one of seven urines positive for morphine, while external subjects in the same treatment condition produced three morphine-positive urines out of seven. Thus, it could be argued that this technique has promise. However, it would seem that only motivated heroin-abusing clients would undergo such a treatment. Unfortunately, these two conditions do not often occur simultaneously. The apparent use of only one therapist (the senior author) is a potentially potent confounding variable, and the short follow-up period does not provide clinically relevant data.

Hirt and Greenfield (1979) used implosive therapy to decrease anxiety and facilitate detoxification in methadone patients. Implosive therapy is based on the assumption that anxiety attached to specific events, such as detoxification, can best be eliminated by repeatedly presenting the subject with imaginal cues which elicit high levels of anxiety without actual adverse consequences, until the anxiety is eliminated. The rationale is similar to that seen in the use of relaxation training: that the internal cues associated with decreasing methadone dose have become conditioned due to aversive withdrawal experiences in the past, and motivate drug use to reduce anxiety. Twenty-four clients were randomly assigned to either implosive therapy, eclectic counseling, or no

treatment. Both the implosive therapy group and the eclectic counseling group met for 12 individual sessions over 6 weeks, followed by a 6-week follow-up period. Methadone dosage was significantly lower at week 6 and during weeks 8 to 12 for the implosive therapy group. Attrition rates were not reported. Small group size, the short follow-up period, and the use of only one therapist (again apparently the senior author) mean that these data can be only suggestive.

Recruiting methadone clients into psychological interventions is difficult. Recruiting them into treatments which use stressful procedures would seem even more difficult. Both covert conditioning and aversion are subjectively stressful. Unfortunately, neither Snowden and Rosenbaum nor Hirt and Greenfield describe their recruiting procedures in detail.

Two studies which have more immediate clinical relevance have also been reported. Bigelow et al. (1976) randomly assigned 60 clients to either contingency management, behavior therapy, both, or neither, in a 2 (contingency management vs none) x 2 (behavioral therapy vs none) factorial design. Behavior therapy techniques included desensitization assertiveness training, relaxation, biofeedback training, and yoga. Contingency management included reinforcement, token economies, contingency contracting, and shaping procedures. Comparisons of data obtained at baseline and at 6 months on 60 clients who completed 6 months of treatment (77.9 percent of the original sample) indicated no differences in the four groups on measures of employment, drug use, and counseling attendance. Attrition rates by groups were not given. The investigators attributed the negative findings to variability among clients, poor quality, and minimal amount of the treatment, which was applied by paraprofessional staff.

The second is the study by Woody and his colleagues in this volume comparing cognitive behavioral and supportive expressive psychotherapy, reviewed under psychodynamic psychotherapy. In the cognitive behavioral condition, clients were helped to identify false beliefs, unhealthy mood states, and problem behaviors. As was the case with supportive expressive therapy, preliminary data indicate that cognitive behavioral therapy may be useful, especially to clients high in psychopathology. As was mentioned above, preliminary data indicated a tendency for clients to be relatively more involved in psychodynamic as compared to behavior therapy.

In summary, evidence for the usefulness of behavior therapy techniques is not strong. However, the field of "behavior therapy" includes many techniques, several of which may be applicable to the problems of methadone maintenance clients. Also, it should be noted that most of the techniques evaluated in methadone maintenance, implosion, covert, and relaxation training are ones which current data suggest are of only moderate usefulness in other therapeutic settings. Other behavioral techniques have been found to be of greater usefulness in other areas. Relapse prevention skill training may prove to be an especially useful modality when used as an aid to detoxification. Studies by Chaney et al. (1978) with alcoholics, and our group with tobacco dependent clients (Hall et al., unpublished), are promising concerning actual decreases in relapse when the technique is taught to motivated clients. Only relaxation training has been given an adequate test. Other modalities have either been tested in limited studies, or final data on their efficacy are not yet available.

The research methodology on behavioral interventions is progressing. In the past 10 years, it has moved from uncontrolled case studies to small-scale, short-term projects to clinical trials which include multiple objective measures, relevant control groups, attention to client characteristics, and follow-ups of sufficient length that differences can be adequately evaluated. However, refinements are clearly possible. Issues of therapist effects and attentional controls have not been addressed. Also studies reviewed have been remiss in neglecting adequate measures of whether the behaviors taught to clients were learned, and if so, whether they were actually used.

Vocational Rehabilitation

Other than psychotherapy, services offered in methadone maintenance programs have included legal and dental services, medical care, child care services, and educational and vocational services. There are several studies on vocational rehabilitation interventions, but I could find no systematic data on the efficacy of other services in methadone treatment.

A survey study by Hargreaves (1980) of three methadone clinics in the San Francisco Bay Area suggested that legal, vocational, and educational services were those

most desired. Of 19 activities listed, legal problems, job help, educational services, and job experience were the top four. Over 50 percent of those surveyed expressed a strong interest in them. In this respect, there may be some discrepancy between clients' self reported needs and clinic services. In a survey of 194 methadone, residential, and drug free treatment programs, Hubbard and Harwood (1981) found that only about two thirds of the clinics provided employment counseling to clients. Over half the clinics had no identified budget for vocational services, and fewer than one in five could identify vocational specialists on their staff, suggesting the vocational counseling offered may have been of less than optimal quality. Despite this lack of internal resources, clinics were not aware of external resources, and did not use them extensively.

Three studies speak directly to the applicability and efficacy of vocational rehabilitation efforts in methadone maintenance. Among the earliest of these was the Wildcat demonstration program (Friedman 1978), which evaluated the effects of supported work on 604 drug treatment clients, about 80 percent of which were from methadone programs. Clients referred to the program were randomly assigned to either supported work placement or to a control condition in which subjects were not offered employment. Criteria for acceptance into the study seem to have varied across time, but appeared minimal, including a referral from a treatment program and appearance at the interview in passable clothes and not intoxicated on drugs or alcohol. Supported work included participation in a special work crew of peers, counseling on and off the job, clear definition of rules and tasks, frequent evaluation, gradual increase of stress and expectations, and frequent rewards. Apparently not all elements were available for all clients, since some were placed without work crews. Varying kinds of efforts, all of limited success, were made to place participants in nonsupported jobs. Clients were interviewed at intake and during the following 3 years. Interview information was verified against other data sources. Data were reported for 194 experimental subjects and 207 controls. Thus, about one-third of the original sample was lost. Included in this one-third are 30 experimental clients who failed to take the job assigned to them. The major findings were that Wildcat clients worked more and earned more than controls. This was especially true while they remained in supported work. During the first quarter of the 3-year follow-up, all experimental subjects worked, but only one in five controls. By the

final quarter of the study, only 49 percent of the experimentals worked full time, about half in Wildcat jobs. Full-time employment in the controls had risen to 36 percent. Experimental subjects used welfare less throughout the 3-year study period. Experimental subjects were more likely than controls to be in a marital or common-law relationship during year 1 (53 percent vs 35 percent) but these differences had largely disappeared by year 3. No differences were found in drug abuse. Overall, then supported work appeared to have a positive impact on several variables, but primarily during the period when supported work was available. However, even this qualified interpretation of the results is weak with such a large proportion of the sample lost, particularly since 30 of the 108 experimental subjects lost had selected themselves out of the sample by not appearing for work. It seems reasonable to assume these were the least motivated clients, and their exclusion probably artificially increases the differences found between the two groups.

TREAT (Training, Rehabilitation, and Employment for Addicts in Treatment) (Bass and Woodward 1978) recruited subjects from a large, multimodality drug treatment program and randomly assigned them to either CETA training (N=95) or to a control condition (N=100). Experimental clients were more likely to decrease drug use, as indicated by urinalysis, and show better outcome on a multicomponent measure of treatment outcome, but showed no differences in treatment retention or in criminal behavior. Experimentals spent more time in full-time work than controls (20 percent vs 14 percent), and earned higher salaries, but there were no differences in weeks worked. No specific data on methadone maintenance clients were presented. Interpretation of the results is confounded by the procedure used for experimental dropouts. Results were reported for the entire control condition. In the experimental condition, 17 early dropouts were replaced, and not included in the data presented, thus biasing the sample in favor of the experimental condition. Later dropouts were not replaced. Also, differences between the conditions may have existed prior to the intervention. Twenty-one percent of the experimental subjects, and 35 percent of the controls, had not worked in the 2 years prior to study start. Other research (Hall et al. 1981b) has shown that no recent employment history is a powerful predictor of failure in job-seeking.

In the random assignment, supported work project of the Manpower Demonstration Research Corporation, approximately

1,200, or 12 percent of the 10,043 participants, were ex-addicts (Board of Directors, Manpower Demonstration Research Corporation, 1980). Over half the exaddict sample (54.2 percent) were drawn from methadone maintenance clinics. Subjects in three cohorts were followed for 1, 2, and 3 years, respectively, depending on time of admission. At the end of the 12-month supported work period, clients were assisted in finding employment. All subjects who completed random assignment and who could be located were included in the final data analyses. A substantial number of clients appeared to be lost to follow-up, since 1-year follow-ups, which were completed for all available subjects, provided data on only 974 subjects. The findings were complex. As would be expected, during the supported work period, experimental subjects worked more hours than controls, and had higher employment rates. Interpretation of the follow-up data was clouded by differences between cohorts entering the program at different time periods. In general, differences were only significant for early entrants, primarily because of lower employment rates among early controls. The investigators found few differences in individual characteristics between late and early entrants, and attributed the cohort effect to differing economic conditions. Participation had little long-term effect on welfare. Initial differences disappeared during the post-supported-work period. Supported work did not influence drug and alcohol use. However, arrest rates were less for the supported work condition, especially during the period immediately following supported work. Outcomes tended to be relatively better for methadone maintenance clients than for drug free clients.

We have completed a series of small scale studies to test the usefulness of a "job-finding" intervention for drug treatment clients. The Job Seeker's Workshop (Hall et al. 1977b; Hall et al. 1981a, b) is a behaviorally based skill training program designed to assist ex-heroin addicts in increasing job interviewing and finding skills. Two of these studies (Hall et al. 1977b; Hall et al. 1981b) drew subjects from methadone maintenance clinics. In the initial study, 49 clients seeking either jobs or placement in a competitive skill training program were randomly assigned to the workshop or to a minimal treatment control. Workshop content included videotaped role playing, experience in completing a job application, and in specific job search procedures. At the end of the workshop an interviewer, blind to experimental conditions, rated subjects with respect to employability/acceptability as a trainee.

At 3-month follow-ups, 50 percent of the experimental subjects and 14 percent of the controls had found employment or placement in a training program. Placement was verified by counselor collaboration and other sources. Also, Job Seeker's Workshop clients were rated more favorably on both interview skills and completed application forms than were the control. Including dropouts (N=4) and those lost to follow-up (N=3) as unemployed in the comparisons does not change the level of significance between the two conditions, although it does reduce the overall employment rate in both groups. In a second study, 60 job-seeking subjects were assigned to either the workshop or to the minimal contact (information only) control. Subjects were assessed by two "blind" interviewers at treatment termination on a multi-item scale tapping specific interview behaviors. Experimental subjects were rated more positively than controls, particularly in terms of general interview competence and manner of self-presentation. Subjects were contacted monthly, and employment verified. By the end of 3 months, 52 percent of the experimental subjects were employed, as compared with 30 percent of the controls. Four experimental subjects left immediately following information presentation and therefore never received the experimental treatment. If they are excluded along with their matched controls, differences in employment rates are statistically significant. If all subjects entering the study are included, differences narrowly miss traditional levels of significance. Differences were found among leaders in effectiveness, but we were unable to identify the characteristics related to effectiveness. Experience did not seem to play a role, since outcome for the most experienced leader was the poorest. Employment rates in the second and the first study for subjects are similar when the only job seeking subjects in the first study are included.

Taken together, these data indicate that the Job Seeker's Workshop has promise as a modality to increase employment in methadone maintenance clients over that occurring when standard services are offered. The studies do not address the possibility that increased attention and expectations alone may account for this increase. Apparently some individuals are better than others at leading the workshops, but we do not know how good and bad leaders differ. The Job Seeker's Workshop was designed to increase job finding. This is a limited goal. The studies did not address the issue of quality of job, wages, or, of greater importance, the amount of time for which the job was held.

Presumably, "job-holding" might require an entirely different set of behaviors than job-seeking, and might be modified by a similar set of treatment techniques.

In summary, vocational rehabilitation has an important place in methadone treatment, especially to clients. Yet many clinics are unable or unwilling to provide it. Also, it is unclear precisely what forms of vocational assistance would be most valuable. Supported work programs may have produced some positive results, especially during the period when supported work was available. However, methodological problems have been so overwhelming that the data are less compelling than one might hope. On the other hand, specific targeted interventions can lead to increases in independently obtained employment, but work has been limited in scope. Given the funding constraints operating in most of the country, supported work may not be practical. Small targeted interventions may be more cost effective.

In methodology, the sheer magnitude of the studies of vocational rehabilitation is striking. The sample size in several of them is great enough that it is difficult to imagine monitoring experimental procedures so that significant deviations did not occur over time and across sites. Such deviations increase variance, and could have attenuated the findings. A second problem is precise specifications of the interventions themselves, especially in staff contact and peer group support. This is especially a problem in multi-site studies, where it would seem there are significant variations across time and from site to site. The field might be better served by smaller-scale studies, similar in magnitude to those found in the psychotherapy literature. There is also a need to investigate mechanisms by which change occurs, and to better link the actual content of the interventions with outcome. Differences in outcome as a function of intervention leaders have rarely been addressed, and no studies compare different treatments or attentional controls, so far as I could find.

THE TREATMENT ENVIRONMENT

Program rules and sanctions, staff background and expertise, and staff and clients' attitudes about methadone treatment are part of the larger treatment environment. While specialized services will generally affect a small portion of a program's clients, the atmosphere of the

program, and the structure in which treatment is conducted, affects all clients, as well as staff. Because these aspects of treatment are so pervasive it is likely that the general program environment explains a large proportion of the general treatment outcome variance.

Contingency Systems

Contingency systems bridge the gap between individual change and system interventions, since they can be instituted for individual clients or can be used on a clinic-wide basis as a general treatment structure. Most writers consider contingency systems part of behavior therapy. Theoretically, this is the case. On the operational level, however, it is more useful to consider these systems are contributors to the treatment environment, since in other fields, at least, it is in interventions involving whole clinics and institutions that contingency management has been most frequently used (for example, Allyon and Azrin 1968). An underlying assumption in contingency systems is that environmental reinforcement contingencies determine behavior. Behavior can be changed by changing contingencies. It is implicitly assumed the clients possess the skills needed for more adaptive behaviors, but are not sufficiently motivated to perform them. Often, reinforcers and punishers from the natural environment are translated into token economies or point systems, where socially desirable behavior (e.g., termination of heroin use) earns points or tokens which can then be exchanged for one or more attractive events which the treatment system can provide (e.g., take-home doses, or self-regulation of methadone dose).

Advocates of contingency systems maintain that every treatment unit provides contingencies for client behavior. However, they argue these contingencies are often ineffective or countertherapeutic, because treatment personnel are not aware of the subtle effects of contingencies on behavior. To be effective, it is generally assumed that contingencies must 1) be primarily positive, since negative contingencies frequently cause efforts at counter-control; 2) occur soon after the target behavior, or be mediated by points or tokens so that the client perceives that his or her behavior has been reinforced; 3) be governed by consistent, explicit rules; and 4) use as reinforcers events that are valued by the client whose behavior is considered "change worthy." By these criteria,

the common clinic practice of involuntary treatment termination following several months of morphine-positive urines is ineffective contingency management. The event (loss of treatment) is negative, far removed in time from the actual undesirable behavior, and frequently occurs as a function of ill defined rules.

Early work on contingency systems in methadone treatment in Sweden was reported by Melin et al. (1976). It is of only marginal relevance because it was conducted on an inpatient ward, and primarily involved reinforcement of ward maintenance behaviors such as bedmaking and getting out of bed. Another early study was that of Hall, Cooper, Burmaster, and Polk (1977a), who treated six methadone maintenance clients in a controlled, singlesubject reversal design. One problem behavior was identified for each client. Target behaviors were heroin use, arriving on time to work and clinic, weight gain, and for two clients, weight loss. Reinforcers were home delivery of methadone, "late" privileges at the clinic, tickets to special events, special food, bus tokens, lunches or dinners in restaurants and, if the subject was on probation, time off probation, and less frequent reports to probation officers. Evidence for the efficacy of the reinforcement system was noted when heroin use, and days on time to work and to clinic were target behaviors. Weight loss or gain were not affected by the treatment intervention.

A systematic program of carefully controlled research on contingency systems has been conducted by Maxine Stitzer and George Bigelow at Baltimore City Hospital. The starting point for this group was the controlled outcome trial (Bigelow et al. 1976), reviewed earlier in this chapter, which found no overall treatment effects for behavior therapy or contingency management. From these data, Bigelow et al. presented five uncontrolled case studies, three of which showed therapeutic changes in either heroin use or illicit benzodiazepam use as a result of contingency management. In subsequent work, 53 clients were surveyed about the attractiveness of potential reinforcers. Take-home doses, receiving $30, receiving $10, and dose self-selection were ranked as most desirable, while activities such as playing pool or participating in a monthly party were minimally attractive (Stitzer and Bigelow 1978). These results replicated an earlier study of Yen (1974). As the authors point out, verbal report of reinforcing efficacy is not always correlated with actual efficacy. Stitzer et al. (1979a) allowed supplementary methadone self-administration in order to determine

whether dose alteration actually served as a reinforcer, or affected symptomatology. Twenty-three subjects were offered the opportunity to alter their methadone dose on a single day as much as ± 20 mg. Dose increases were chosen on 94.3 percent of occasions, and largest available increase on 76.6 percent of these. These data indicated that dose increases were potentially attractive reinforcers.

Stitzer et al. (1977) demonstrated that take-home doses can be used to increase attendance at counseling sessions in chronic nonattenders. Sixteen subjects, selected on the basis of low attendance rates, underwent five successive 2-month periods when weekend take-home periods were either contingent on attendance at counseling or were given to all subjects independent of attendance. During contingent delivery periods, attendance increased significantly above levels observed during noncontingent periods. During noncontingent periods, attendance rates did not return to the same low level observed during the baseline phase. Follow-up data were not presented.

Much of the work of this group has focused on reduction of illicit drug use with contingencies. Stitzer et al. (1980) assessed the effects of a limited contingency "menu" on heroin use. Seven male clients who consistently produced morphine-positive urines during a baseline period participated in a reversal design, where morphine free urines were reinforced. Reinforcers used were a choice between $15, two methadone take-home privileges, or two opportunities to self-regulate dose. During contingent reinforcement, the rate of morphine free urines declined significantly. However, the morphine-positive rate during randomly interspersed noncontingent weeks also declined, so the difference between contingent and noncontingent weeks did not reach traditional levels of significance. At a repeat baseline after study completion, use rates returned to baseline levels. On 95 percent of the occasions, clients chose money as a reinforcer. All remaining reinforcer choices were for take-home doses.

The final two studies from this group addressed the use of illicit benzodiazepines among methadone maintenance clients. In the first (Stitzer et al. 1979b), eight chronic benzodiazepine abusers were given prescriptions for 20 mg diazepam daily. If they refused this diazepam dose, they were given the opportunity for one take-home dose, or to self-regulate their methadone dose for a day. During

baseline, 95.6 percent of available diazepam was requested. Only 11.2 percent of diazepam was requested when refusal resulted in take-home doses, and 69.7 percent when methadone dose self-regulation was available. There was no noticeable trend in use of illicit benzodiazepines or other illicit drugs throughout the study. Take-homes appear to be more reinforcing than does self-regulation, at least than the 20 mg dose changes offered in this study, or the opportunity for a one-time increase. Different results might be found with different dose levels, or a greater number of increases. Unlike counseling session attendance and heroin use, requests for the diazepam prescription rapidly returned to baseline levels when the reinforcers were eliminated. This methodology was extended to out-of-clinic illicit benzodiazepine self-administration in a subsequent study (Stitzer et al., unpublished). In 10 diazepam abusing methadone maintenance clients, benzodiazepine free urines were reinforced by a choice of two methadone take-home doses, $15 cash, or two single-day opportunities to self-regulate dose. The efficacy of the contingencies was evaluated in an A(baseline)-B(treatment)-A(baseline) design. In five of the ten subjects, benzodiazepine use decreased during treatment, and returned to baseline levels during the second baseline. Three other clients showed runs of five to eight consecutive clean urines during the intervention period. Clients selected the methadone take-home privileges on 37 percent of the occasions when incentives were earned, and money on the remaining 63 percent.

The small-scale, well controlled studies of Stitzer's group provide evidence for the possibility of contingent control over problem behaviors shown by methadone maintenance clients. The clearest results appear to be those obtained with diazepam abuse. Effects for counseling attendance and heroin use were less clear, since increased attendance was noted during noncontingent as well as contingent phases. Since these behaviors return to baseline levels if a repeat baseline is included as the final phase of the study, it is quite possible a Hawthorne effect is operating. Reinforcement contingencies would be no different during the repeat baseline than during mid-study noncontingent periods. What is different is the client's perception that he or she is part of a special study group.

Reversibility is the paradox of demonstrations of reinforcer effectiveness. To demonstrate reinforcer control, the researcher must be able to show that the effect in question is reversed when the contingencies are reversed

or eliminated. This is essentially demonstrating relapse. To be convincing as a clinical tool, it is necessary that the adaptive changes occurring during contingency management be shown to last over long time periods. Comparisons with controls given the same amount of staff contact, as well as with those given noncontingent reinforcers, are also needed. Also, the studies by the Baltimore group have been completed in a small, research oriented clinic. Comparative studies of contingency systems in more typical treatment clinics are needed to establish the generalizability of these findings. As far as I could tell, no subject has dropped out of the Baltimore studies, although some subjects have been lost when they left the treatment clinic. A treatment/no-treatment comparison would allow determination of dropout rates. One would expect they would be small, since only positive reinforcers are offered.

Data obtained by Havassy indicate possible programmatic limitations of contingencies systems (Havassy et al. 1979; Havassy and Hargreaves 1981; Havassy and Tschaan, 1982). One hundred sixteen subjects from two methadone maintenance clinics were randomly assigned to either dose self-regulation, self-regulation with incentives for dose reduction, or to a standard treatment control for 48 weeks. In the self-regulation condition, subjects could decide weekly how much methadone they wished to receive within certain limits. In the self-regulation plus incentive condition, clients also gained additional take home privileges according to an incentive schedule. The greatest take-home privileges which could be earned were 2 weeks of take-home doses. In the standard treatment control subjects received standard clinic treatment. No reinforcement effect was found in this study, even among the subset of clients on voluntary detoxification.

There are several differences between Havassy's study and those of Stitzer and Bigelow which may explain differences in outcome. First, as Havassy and Hargreaves (1981) note, shortly after initiation of the study, the clinics became enmeshed in long-term administrative and political turmoil which extended the life of the study. Although the delivery of treatment and incentives was monitored by research staff, the effects of such chaos may have been such that experimental effects were swamped. Second, while Stitzer provided take-home contingencies against a standard clinic policy of no take-homes, Havassy's clinics had the standard Federal Methadone Maintenance Clinic Regulations in

effect, wherein subjects were allowed up to five take-homes per week by virtue of time on the program, absence of evidence of use of illicit drugs, and "leading a productive life." Thus, the contrast between conditions may have been subjectively much greater for clients in the Baltimore studies. Finally, extended periods of time away from the clinic (e.g., 2 weeks) may not have been reinforcing for many clients who use the clinic as an emotional and social base.

Despite the moderate promise of contingency management as a tool in methadone maintenance, use of contingency management does not seem widespread among methadone maintenance clinics. No doubt there are several reasons for this, including resistance to use of contingencies because of philosophical distaste, lack of staff expertise to design and carry out effective contingency management, or perceived expense. Staff who believe that contingency management somehow decreases client freedom, or find the systematic use of reinforcers somehow incongruent with their world view will probably never be able to mount effective systems within their clinics. Work in other areas has shown that nonprofessional staff can be trained to apply contingency management procedures, although the amount of staff training and the posttraining monitoring often greatly exceed the amount anticipated. Most of the reinforcers used in the studies reviewed are part and parcel of the clinic operating system, and thus are available for use at the clinic for no cost. Even when external contingencies such as payments have been used, the cost is often low. For example, Hall et al. (1977a) estimated that the median cost of reinforcers per week per client in their study was $2.69, and noted that many reinforcers, such as game and show tickets, could be obtained free from charitable organizations. As many clinics shift to a fee-for-service basis, it is not inconceivable that some small portion of that fee could be part of a "contingency fund" which is used when external contingencies are required.

Treatment Structure

Simpson et al. (1978) suggested that the treatment structure of programs can be divided into two categories, "adaptive" and "change oriented." Unlike contingency systems, these treatment structures are not derived from formal theory, but developed out of the treatment community's experiences with methadone clients. "Adaptive" programs regard drug abstinence as a long-term, ideal goal, but

stress the importance of adapting treatment to the immediate needs of the client. Doses and other treatment requirements reflect minimum structure and low demand. "Change oriented" programs emphasize the goal of eventual abstinence from drugs and the need for resocialization. Treatment in these programs is more structured and involves a higher level of intervention in clients' activities. Differences in outcome between these two types of programs were examined in the Drug Abuse Reporting Program (DARP) study, a nationwide project focused on the effectiveness of drug treatment. The purpose of the evaluation effort was to determine the effectiveness of methadone maintenance, therapeutic communities, outpatient detoxification, and outpatient drug free treatment, all self-selected, with an intake-only comparison group. Treatment type was determined by the interview data collected from treatment personnel at each agency. Eight hundred black and Caucasian males were in the original sample. Of this sample, between 653 and 658 were available for follow-up data collection. (The number varied depending on the information collected.) Data were reported for the first posttreatment year only. In the first year posttreatment, methadone treatment type did not significantly predict differences in outcome measures, which included objectively verified interview estimates of drug use, employment, and criminality. This lack of differences existed despite the verbal statements of philosophy and goals.

It is difficult to put a great deal of faith into an interpretation of these data, since treatment structure would seem especially vulnerable to confounding by preexisting client differences. For example, programs which attract more recalcitrant clients may gradually be shaped into more restrictive and "change oriented" policies. Further, it is unclear how precise the descriptions of the treatment environments actually were. Also we do not know what staff practices and behaviors actually occur within the differing program types. It may be that, given the regulations governing the provision of methadone treatment, and the constraints of funding, little opportunity for differences in staff behavior exist.

McGlothlin and Anglin (1981) reported a 6- to 7-year follow-up on admissions to three methadone maintenance programs. Three hundred forty-seven subjects were included in the study sample. Two of the programs used a high-dose, long-retention policy; the third used lower doses and a stricter policy about involuntary terminations. The first two programs seem to represent the adaptive type of

Simpson et al.; the latter parallels the change oriented type. Subjects were interviewed, and a urine specimen collected. Only 10 percent of the living subjects were not interviewed at follow-up. The data overwhelmingly favored the high-dose, long-retention program in arrests, incarceration, narcotic addiction, and self-reported criminal behavior. These differences were found both during treatment periods and during periods without methadone.

The most common interpretation of these data is that retention in treatment and higher doses result in better treatment outcome. This is plausible. However, the programs were evaluated post hoc, and it is not known how different staff attitudes and client expectations moderated outcome. The most conservative conclusion is that some factor associated with participation in high-dose long-duration programs does appear to result in better outcome. Whether this occurred because of differences in dose, treatment duration, or staff or client attitudes resulting from or mediating these program differences is not known. Because of the possibility of an interaction between client type and treatment structure, it would seem that questions of this sort can ultimately best be answered by random assignment studies, which include a strong process component. The latter would be needed to carefully map the differences in behavior between the two types of programs. Alternately, multiclinic correlational studies with extensive descriptive and process components would be useful.

Another aspect of treatment structure is the degree to which the Federal regulations for methadone clinics are enforced, and the extent to which such enforcement influences outcome. Havassy and Hall (1981) examined one aspect of these regulations, the urine monitoring system, in a controlled study. Methadone maintenance clients (N=431) from four clinics were randomly assigned to either a standard treatment control, in which the standard urine monitoring procedures were enforced, or a no-monitoring condition, where urine monitoring was suspended for 1 year. At two points during the year (month 4 and month 8), unannounced urine samples were obtained and analyzed for opioid and nonopioid drugs. There were no significant differences between the groups, despite a large enough sample to detect small differences, were they to exist. Again, this research supplies no answers about why differences were not found.

Theoretically at least, the urine monitoring system should function as a contingency system of sorts, since program privileges and even treatment continuation are supposedly linked to the results. The reason for the failure of the system to affect drug use, when contrasted with the effectiveness of experimental contingency systems, may lie in both the nature of the contingencies provided, and in the actual staff behavior. In the Stitzer et al. contingency studies, reinforcers were positive. Clients could earn privileges over and above those available to the majority of clinic clients if they modified their behavior. In practice, the urine monitoring system at best is a mixture of positive and negative consequences. It is mostly seen as negative by clients. Many methadone treatment clients have a lifetime history of negative consequences impinging on them, and have both become accustomed to them and adept at avoiding them. Also, the actual implementation of the regulations in the Havassy and Hall study is not known. In the carefully controlled studies of Stitzer et al., usually around 90 percent scheduled contingencies were correctly delivered. I would imagine this figure would be much lower for staff in large clinics, using an externally imposed system without a great deal of commitment to that system.

No other aspects of treatment structure have been studied systematically. Patch et al. (unpublished) reported their experience from one clinic when take-home doses were abolished. Discharges increased five-fold in the month following the implementation of the no-take-home policy, and thereafter leveled off to about twice the baseline rate. Although Patch et al. reported employment data following the elimination of take-home doses, I found it impossible to interpret these data, due to the case study nature of the report, and change in the general employment picture which occurred during the time span studied.

Staff Training

As Brown and Thompson (1975) have commented, drug treatment administrators have been more than willing to make use of former clients as counselors. Clients value them as much, if not more than professional counselors (Ball et al. 1974; LoSciuto et al. 1979a). The role of the exaddict counselor has been a controversial one since the early days of drug treatment. Exaddicts have been seen as essential in reaching the addict, gaining confidence, and facilitating entrance into treatment (Cuskey and Premkuman

1973). Exaddicts were also seen as better able to detect treatment progress, or lack of it, and knowledgeable about both the ways and weaknesses of drug treatment programs, and of the street. These positive views were balanced by negative ones: lack of training, overidentification with clients, and righteousness over their own success have been mentioned as problems (LaRosa et al. 1974).

LaRosa et al. randomly assigned 42 methadone clients to therapy groups led by either master's level therapists or exaddict counselors. At the end of 1 year, the master's level therapists retained more clients in methadone treatment (68 percent) than the exaddicts (40 percent), a difference approaching traditional levels of significance (.066). Also, clients expressed more dissatisfaction with exaddict leaders. However, ethnic differences in the counselors and clients may have confounded the outcome. The master's level therapists were Caucasian, the exaddicts were black, and the clients were primarily Caucasian.

Brown and Thompson (1975) compared 52 clients assigned to 29 nonaddict counselors to 84 clients assigned to 30 exaddict counselors. Subjects were recruited from a multimodality program, which included methadone treatment. Care was taken to select only clients who had been assigned to one type of counselor exclusively for the course of their treatment career at the program. Neither the clients nor their counselors were found to differ on demographic variables. Clients were compared on measures of adherence to the program regimen, nonuse of illicit drugs, employment, and absence of arrest. All these measures were taken from program or external records. No differences were found between the two conditions. More of the exaddicts' clients had been arrested as compared to the nonaddict counselors (41.66 percent vs 26.92 percent), and fewer were employed (57.14 percent vs 70 percent), but these differences were not statistically significant. The authors found the lack of differences congruent with earlier research, which indicated that formerly addicted and nonaddicted counselors interpreted their roles similarly (Kozel and Brown 1973). The positive features of this study were objectively verified outcome measures and elimination from the sample of clients who had been treated by more than one type of counselor. On the other hand, the use of a correlational design weakens the strength of conclusions which can be drawn about the relationship between counselor type and client outcome.

Longwell et al. (1978) reported outcome similar to that of Brown et al., but used only one outcome measure, urinalysis result. Counselor effectiveness for 253 clients and 26 counselors was evaluated. Clients were divided into six groups, including those with 1) multiple exaddict counselors; 2) multiple nonaddict counselors; 3) exaddict and nonaddict counselors; 4) a single nonaddict counselor; 5) a single exaddict counselor; and 6) those without a counselor for 1 out of 3 months. Only the last group differed from the others. Clients without counselors for one-third of the study period showed more opiate-positive urines than those in the remaining five groups.

An issue related to the use of exaddicts is the use of paraprofessionals in general. Many individuals without advanced degrees in health services have come to drug treatment from alcohol abuse and mental health fields, and have counseling positions within drug treatment. Connett (1980) failed to find general differences in patient progress on use of illicit drugs, attainment of drug free status, employment, time in treatment, or take-out dose level 6 months after treatment as a function of counselor assignment in 303 clients assigned to either paraprofessional (average education level of 12.7 years) or professional counselors (master's level). However, the professional counselors may have been assigned more difficult clients. At admission, 44 percent of the paraprofessional counselors' clients were abusing illicit drugs other than heroin, as compared to 70 percent of the professionals' clients.

LoSciuto et al. (1979a, b) investigated the activities, attitudes, and clients outcome of professional, paraprofessional, nonexaddict counselors, and paraprofessional exaddict counselors. Eighty-two counselors, 29 administrators, and 302 clients were interviewed in nine methadone maintenance and six drug free programs throughout the country. Clients were interviewed at two times during the study, at least 1 month after they began treatment with the counselor, and 4 months later. Treatment programs were methadone maintenance and drug free. Professional counselors were those with at least a bachelor's degree who did not have addict backgrounds. Paraprofessional counselors of either group had less education, and, of course, the exaddicts had to have a history of addiction. Overall, there were few differences between the counselor types either in activities, attitudes, or client outcome. It is of some interest that relevant education, particularly counseling courses, did not differ greatly between

between the counselor types. Professional counselors were more likely to be Caucasian, female, younger, and to have had a briefer tenure in their present position than the other two groups. Paraprofessional counselors were more often black males involved in community education, who were more likely to socialize with clients.

Overall, the literature on staff training and experience is consistent. Few differences exist in the outcome of clients of different types of counselors. This conclusion must be drawn with some caution, however, since the only study using random assignment was that of LaRosa et al., and in that instance, group leadership performance, not the traditional counseling role, was assessed. Since at least one investigator found differences in types of clients assigned to counselors of differing backgrounds, it is possible that the lack of differences is due to a confounding of the independent variable with interclient differences which are related to later success. That is, polydrug abusers generally have poorer outcomes in methadone treatment (for example, Perkins and Block 1970; Babst et al. 1971). If professional counselors are routinely assigned more difficult clients, a potentially better outcome for these counselors may be obscured.

By far the most extensive correlational data were collected by LoSciuto et al. However, their definition of a professional does not fit the traditional use of the term. Some specialized training, especially in ethics, conduct, and practice is usually assumed to be part of professional training and rarely, if ever, provided by bachelor's degree programs in social sciences, with the possible exceptions of social work and nursing. Also, in this study it was unclear the extent to which other treatment personnel were involved in the client's treatment. In the studies by LaRosa et al. and LoSciuto et al., differences in counselor classes were confounded by ethnic and sex differences, and the effects of these variables are unknown.

In retrospect I wonder if comparison of this sort, especially between "professionals" and paraprofessionals, is meaningful. Few drug treatment programs can afford to employ many true "professionals," i.e., individuals with master's and doctoral degrees in relevant human services. Some might argue that most programs do not have extensive need for their services. In roles, functions, and relevant training, counselors with bachelor's degrees and those without are so similar it is unlikely an important

difference exists. On the other hand, the role of the exaddict counselor needs more exploration. No one is qualified to provide drug treatment services simply by virtue of having abused drugs. What is important is how that experience is translated into client services. Some expectations of exaddict counselors have been painfully unrealistic. For example, group leadership is a learned skill, and there is no reason why a counselor should be expected to have acquired this skill simply because he or she has abused drugs and is motivated to help other abusers. Logic and clinical experience suggest that exaddicts are especially effective as facilitators in the transition from the street to the clinic, but I know of no data to support this view. Studies of the unique functions of the exaddict counselor, and where such individuals are and are not effective, do not exist.

Attitudes Toward Methadone Maintenance

A pervasive part of the treatment environment is the attitudes that clients and staff have about themselves and the treatment being offered. While exact links between attitudes and treatment outcome have not been established, it is not hard to imagine how attitudes influence outcome. Positive attitudes should foster eagerness to enter treatment, adequate duration of treatment, and commitment to the treatment program by both staff and clients. Negative attitudes, on the other hand, may well be linked to refusal of treatment even when indicated, to attrition, or to premature detoxification and less than optimal involvement in treatment by both the methadone clients and staff (Brown et al. 1974).

Ball et al. (1974) interviewed 242 clients and 44 staff members of a large methadone maintenance program. Approximately 39 percent of the program staff saw methadone clients as physically ill, but only 20 percent of the clients agreed. Even more striking was the lack of agreement between clients and staff about "mental illness." More than 95 percent of the staff held that methadone clients were mentally ill, while approximately 80 percent of the clients did not see themselves as mentally ill. Staff and clients also disagreed about the clients' treatment goals. Forty-four percent of the clients saw the clients' treatment goal as "getting off drugs," while only 29 percent of the staff believed methadone clients enter treatment for this reason. These percentages are reversed for clients; 26 percent of the clients felt methadone clients'

goals are to "keep from being sick," in contrast to 45 percent of the staff. Furthermore, 71 percent of the staff saw addicts as difficult to treat, but only 33 percent of the addicts agreed with them. As Ball et al. comment, this disparity is the ideal climate for the development of a therapeutic impasse. Clients and staff fall into two different factions, and treatment degenerates to a "silent war." So far as I could find, no attempt has been made to replicate these results more recently, or in other locations.

In a series of studies, Brown and his colleagues investigated the attitudes of drug treatment staff and clients towards heroin addicts, abstinent exaddicts, and methadone clients. Brown et al. (1972) asked drug treatment staff (N=23), methadone-maintained clients (N=35), and abstinent clients (N=20) to characterize addicts on heroin, abstinent exaddicts, and exaddicts on methadone, on the Adjective Checklist, a standard 300-item inventory which yields scores on 15 personality traits (Gough and Heilbrun 1965). The three subjects' samples differed little in their descriptions. All saw addicts on heroin as less responsible and conscientious, less concerned with achievement, and less understanding and supportive of others. Difference in perceptions of abstinent addicts versus those on methadone are particularly interesting. Methadone clients characterized addicts on methadone as less dominant, independent, and persevering than abstinent addicts, and less insightful and caring for others. Abstinent addicts agreed. They also saw the methadone clients as more aggressive and in need of support from others. In a second study (Brown et al. 1974), four staff samples, including administrators and supervisors, exaddict counselors maintained on methadone, abstinent exaddict counselors, and nonaddict counselors (N=88) were also asked to describe addicts on heroin, those abstinent, and those on methadone on the Attitude Checklist. The results were similar to those of Brown et al. (1972). Abstinent addicts were categorized as forceful, striving, and possessing a capacity for self-understanding. Methadone clients were seen as comparatively submissive and self-effacing. Three years later (Brown et al. 1975), staff and client attitudes toward the same three addict groups were again assessed. The Attitude Checklist was once again administered to three samples, including clients of detoxification/abstinence centers, methadone maintenance centers, and staff at these centers (N=135). Comparison of profiles of attitudes between 1970 and 1973 showed

little change in conceptions of abstinent addicts and addicts on heroin. However, perceptions of methadone clients differed across time. In 1973, the methadone client was rated considerably lower in measures of striving (achievement, endurance, and order), and somewhat lower on forcefulness in social relations than in 1970. However, the methadone client was also rated as higher on exploration of self (intraception) and on scales indicating strong social needs and recognition (exhibitionism). These data were all collected in one urban location (Washington, DC), with primarily black clients and staff (Brown, personal communication), and it can be argued that these attitudes are unique to that location and ethnic group. However, results consistent with these were found by Sutker et al. (1978) in a survey of therapeutic community, multimodality, and methadone maintenance clients in New Orleans, in a sample which includes both blacks and Caucasians. Sutker et al. asked clients to describe a typical staff member, therapeutic community member, methadone client, and multimodality client. Methadone clients were described as more aggressive, dissatisfied, and less self-confident, independent or achievement motivated, and lowest in general adjustment.

With the exception of the aggressiveness/passiveness dimension, the degree of replicability seen in these studies is convincing. Methadone clients do not see themselves as achievement oriented or striving, but as affiliative and introspective. They do not believe they have the characteristics ascribed to the ideal male in our culture. Treatment personnel agree with them. The extent to which the disparity indicates undesirable characteristics may differ among staff and clients. Assuming male clients agree with the rest of the culture that these are desirable attributes to possess, as one would expect they would, these perceptions might motivate clients to avoid treatment entrance, and to detoxify more rapidly than might be advisable. It is unclear to me what these data mean for female clients, since at least in one study (Brown et al. 1975) they resemble the traditional female stereotype: psychologically minded, socially oriented, nonassertive, and nonachievement oriented.

It is not sensible to critique these studies by the same criteria used for the rest of the chapter. Generally, issues to be addressed in a critique of attitude studies are sample size and appropriateness, and the adequacy of instruments used. These reports seem adequate in this respect. However, they do raise several questions. Among

these are the extent to which staff and clients actually view the assigned characteristics as positive or negative, and the "anchor point" used. For example, differences in age and sex of addict group used as perceptual anchor could produce such differences. Methadone maintenance clients are generally older than clients choosing therapeutic communities. There is evidence that introspection and affiliative needs increase with age (e.g., Bosse et al. 1980). Because of this age difference, methadone clients may really be more introspective and affiliative. Other questions are about generalizability across time and geography: are such attitudes still prevalent, and do they occur in all parts of the country? Other questions concern the extent to which such perceptions are determined by treatment program structure and philosophy, and vice versa. Also, the link between these perceptions and treatment outcome has not been determined.

SUMMARY

Psychosocial Interventions

Clinical Directions. Clinically, we are nowhere near a clear answer concerning the effectiveness of various psychosocial interventions in methadone treatment. Each of the major psychotherapeutic modalities reviewed showed promise in at least one well designed study. While more energy has gone into research on vocational rehabilitation projects, the findings, especially about publicly supported work projects, are less clear. Also, vocational services are virtually the sole service other than psychotherapy which has been evaluated. Parent education classes have been described (Suffet and Brotman 1982; Lief 1981), but not evaluated. I could find no description of legal services. The question of usefulness of "enriched" services versus a simple dispensary model has not been settled. Many clinics do function with minimal services. I wonder if the time has arrived when a controlled study of the effectiveness of these services could be completed. While a random assignment study would be desirable, but difficult, a large-scale correlational study should clearly be feasible, and would provide useful information.

The safest recommendation is for provision of a variety of services in clinics, less because sound research has shown them indispensable than because they are wanted by clients, and the preliminary data are favorable. Some of

these services are not currently available at most methadone clinics. Given current funding constraints, outside referral to outside agencies may be a partial solution. However, outside referral may be less than satisfactory if effective services are the goal. Too often are nondrug community agencies hostile to methadone maintenance clients, or simply ignorant of their unique needs. If referral to outside agencies is to be useful, considerable restructuring of services for methadone clients is essential. No recipe for such restructuring is currently available, but some innovative ideas have recently been offered by Thompson (personal communication), who has proposed a fee for "effective" service-based contingency systems for agencies who effectively serve drug treatment clients referred to them.

Different services may have different groups for whom they are effective (Woody 1981; Rounsaville et al. 1982). Investigators in psychotherapy studies in methadone maintenance have been comparatively thorough in collecting treatment acceptance data, and these data indicate small proportions of the treatment population accept psychotherapy. In some studies, substantial proportions of the acceptors drop out prior to treatment completion. This low use rate is not surprising, nor should it discourage new efforts to offer and study psychotherapy in methadone maintenance clinics. The diversity present in methadone clinics in psychological characteristics and behavior suggests that similar data may well be obtained when acceptance rates for other psychosocial services are collected. Despite these small proportions, provision of such services may be essential if rehabilitation is truly the goal. For example, there is evidence that drug treatment clients high in psychopathology do poorly in traditional drug treatment (McLellan et al. 1983). Thus, psychotherapy may be a necessary if expensive adjunct if such clients are to benefit from treatment at all. Since participation in therapy may be of value, methods to encourage treatment acceptance and continued participation should be explored, as well as innovative adoption of traditional psychological services so they are attractive to methadone maintenance clients.

One unexpected outcome in the studies reviewed is the general effectiveness of brief interventions in methadone maintenance. In some instances, this brevity has been planned (Stanton et al. 1980), while in others, differences have been found between conditions, despite the

tendency of subjects to drop out relatively early in treatment (e.g., Woody, this volume, p. 541).

Research Directions. Methodology in the research on psychosocial interventions, especially the psychotherapies, has reached an exciting stage. After a slow start, well controlled studies are appearing in the literature. While results are sometimes conflicting, the quality of the data is frequently good enough that meaningful treatment variables may well determine these differences, rather than basic inadequacies in research methodology. However, although we have mastered the basics, many more subtle factors, such as therapist intervention interactions, attentional controls, and client-treatment matching remain virtually untouched.

"More well controlled research" is needed in every scientific area ever reviewed, but I would argue that the case is especially pressing for methadone services. After many case studies, and studies that did not survive far enough into the implementation to make it into this review, adequate methodology for outcome research is being developed. In addition, the highly politicized, chaotic atmosphere of early methadone clinics seems to have been replaced by more organized treatment efforts. Clinic disarray is bound to impair the implementation and findings of outcome research (for example, Havassy and Hargreaves 1981), usually by adding to the variance of the study, and thereby attenuating differences between treatment conditions. As such, current clinics may be much better settings for outcome research than those of even 5 to 6 years ago.

The Treatment Environment

Clinical Directions. Overall, the literature on the treatment environment is weaker than that on psychosocial services. It is more difficult to draw conclusions based on the current data. Given this caveat, however, some preliminary assertions can be made.

Contingency systems show some promise as methadone treatment management methods. They can be designed so that costs are moderate. However, research is far from conclusive, and attention placebo effects may well play a strong role in the outcomes observed. Also, staff training and monitoring may be more difficult than they would appear at

first glance. Whether such orderly systems will be effective in the lively atmosphere of the typical methadone clinic is an empirical question.

There is little controlled research on other aspects of treatment structure, including the treatment "style" adopted by a particular clinic, or the degree to which it adheres to Federal regulations. However, my tenuous interpretation of the existing data is that regulations and structure do not make a great deal of difference. They may even be harmful. This conclusion contradicts that concerning contingency systems, which are, after all, structured systems with regulations about the use of environmental events to change behavior. There are two possible resolutions to this paradox. As discussed earlier, it may be that the contingencies in the regulations are ineffective ones, or that the effectiveness of contingency systems does not survive when they are translated to larger treatment environments. I favor the former explanation, since data in treatment of other disorders contradict the latter (for example, Fairweather and Simon 1963; Allyon and Azrin 1968; Bailey et al. 1970).

Staff training and background do not appear to greatly affect treatment outcome, at least in current staffing patterns, where counseling roles and attitudes of social workers, nurses, exaddicts, and nonaddict paraprofessionals are similar. Despite the considerable controversy over the use of exaddict counselors, they appear to do the same tasks as other counselors, with no greater or less effectiveness. A model which capitalizes on the unique experiences of exaddict counselors has not been developed.

Methadone has not been a popular treatment in many segments of the community. Perhaps for this reason, the self-image of the typical methadone client varies from the cultural ideal. This may negatively affect treatment, but the nature and complexities of this relationship have not been studied.

Research Directions. Research on the larger treatment environment has relied heavily on correlational methods. While this is acceptable in some instances, other questions would seem to lend themselves to experimental designs. The latter include the efficacy of different counselor groups, and treatment structure. Random assignment to widely differing treatment modalities, such as methadone vs therapeutic communities, seems doomed to failure.

When great differences are perceived, and potential subjects have a preference, they will destroy the study by refusal to enter it, or by early attrition. However, when the differences are less immediately apparent, as would be the case with counselor assignment or treatment structure, random assignment studies are possible. Random assignment studies of treatment structure are especially desirable, since at least one correlational study indicated that differences exist.

As was the case with intervention studies, I am struck by our lack of knowledge about the mechanisms by which outcome effects occur. For example, if programs with liberal policies about continued treatment do produce better outcome, what behaviors, attitudes, and perceptions do they produce in clients which mediate this outcome?

Finally, many aspects of the treatment environment remain untouched by research. For example, issues of client staff ratio, the usefulness of aspects of the methadone regulations other than urine monitoring, and of program policy have not been researched to any extent. As individual states reshape their respective methadone programs according to local pressures, such information would be of value in determining the way in which these factors act on outcome.

CONCLUSIONS AND RECOMMENDATIONS

1. Research on services in methadone maintenance has only reached the level where designs are sufficiently strong to allow some very tentative conclusions. This is especially the case for the psychotherapy literature. Within each of the three therapy types reviewed, at least one major study has been completed, or is nearing completion, which is both methodologically adequate and also suggests that the treatment evaluated may be of value to selected subsamples of methadone clients. Lacking are adequate attention controls and designs where therapist effects are more carefully controlled than they are in current work. Replications and extensions of findings of interclient variability in treatment sensitivity are also practically nonexistent. The latter is especially important since methadone clients vary so greatly on personality and behavioral characteristics. Within family and behavioral therapies especially, most research has evaluated only a very limited range of techniques. Marital therapy would

seem particularly relevant, since methadone clinics report they offer it more than any other form of family therapy.

2. Research on other ancillary services lags behind that on psychotherapy. Only in vocational rehabilitation, particularly in supported work, has a significant effort been made. However, these studies tend to be large, complex, and not as well controlled as one might hope, and it is difficult to draw firm conclusions about outcome. Supported work does seem of value, especially during periods when it is available. Data on follow-up periods are not at all convincing. Smaller, targeted interventions aimed at specific parts of the rehabilitation process appear promising, but more work is needed to expand this approach to other aspects of the employment process if it is to become clinically important. Research on vocational services might borrow from the methodology of smaller-scale psychotherapy studies. Power analyses to determine sample sizes needed to detect differences, and careful follow-ups of dropouts would add to knowledge about this important element of rehabilitation. Other lacks are studies of services other than vocational rehabilitation, such as enrichment classes (e.g., childcare), dental and medical care, and legal assistance. Also, we still do not know whether or not provision of services adds to the dispensary models of methadone treatment; methodologies are available to answer this question.

3. Contingency management may have promise as a way to structure programs. However, many questions must be answered before the clinical utility of these systems is demonstrated. These include the role of therapeutic attention, and whether therapeutic changes are maintained over longer time periods, and at clinically significant levels. Most research in this area has been small-scale, using within-subject designs. More complex designs which can control for attentional factors are needed, as are studies of implementation in "typical" clinical settings.

4. It is unclear if there are differences in outcome as a function of general treatment structure. Nonrestrictive programs may have better long-term outcome. Reasons for this may include higher doses, longer times in treatment, or some unknown moderating variable. There are no random assignment studies evaluating structural differences, nor are there sufficient data to indicate the mechanism which might affect differences in outcome.

5. Few differences have been found between counselor types and treatment outcome. This is not surprising when one considers the roles and attitudes of counselors in the different types. Most seem to see their job similarly, and engage in somewhat similar activities on the job. Because of these similarities, the question may not be a meaningful one. The unique role of the exaddict needs additional exploration, however. This exploration would best be accomplished in a random assignment study.

6. Methadone clients are seen as less achievement motivated than abstinent exaddicts. In some studies, they are also seen as less aggressive, more social, and more psychologically minded. These perceptions are shared by methadone clients themselves, clients of other modalities, or treatment staff and administrators. The relationship of attitude to outcome should be examined, since it may have a deleterious effect on long-term treatment. Clients of different sexes may be differentially affected by these stereotypes. If outcome and attitude are related, the program and personal characteristics which determine these attitudes should be investigated, and appropriate interventions developed to change them.

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CRITIQUE

Edward Senay, M.D.

This is an excellent piece of work. The author has analyzed a complicated literature in sound, scholarly fashion. I agree with the author's premise that the field has moved from case reports to studies incorporating appropriate blinds, random assignment, and adequate methodology. This permits analysis on a much higher level than was the case when we made decisions on the basis of clinical experience and case report data. The division of the paper into two sections seems to be without any clear rationale, but it is not a serious error. The only major criticism I have of this work is the vagueness of the conclusions and recommendations. After reading the careful, well analyzed reviews of the different variables, I looked forward to the final section but was disappointed because this section lacked clarity. What does the author see as the top priorities for research? In what order? It would add a lot to the paper if the author would indicate how she sees NIDA's priorities for research. I will present mine in the final section of this paper.

In discussing levels of confidence one can have in different kinds of studies, the author makes the statement that aggregate data are on the case study level. This is true to a point. I think that she should add that when aggregate data encompass very large numbers, the level of confidence can rise because the probability of having a sample increases. Data bases as developed by Sells are of a different order than most aggregate data because of the size of his data base.

I have a somewhat parallel comment to make on the author's discussion of follow-up. It is true that relatively short interventions need follow-up until relapse rates hit an asymptote. But as the length of interventions increases, the necessity and significance of follow-up study changes. If, for example, a therapeutic community stay is for 2 years, then one could well content one's self with an examination of relevant variables during the 2-year period. Follow-up could add to the significance of the study but would not be as important as it would be in an intervention lasting a short time--21-day detoxification, for example. It is very costly to carry out effective follow-up studies, and they are not always necessary.

The author, in discussing the problem of attrition, quite properly notes that this problem limits the confidence one can have in research conducted on clinical populations. In the review of Stanton's study of family therapy, the Woody et al. study of various therapies, and the New Haven group's study of short-term therapy, the author seems not to follow through consistently on the limits of these studies directly attributable to the attrition problem. In each of these studies the process of subject selection combined with the problem of attrition precludes generalization.

The review of Stanton's family therapy is excellent. I would add that any discussion of family therapy with addicts should define what is meant by family therapy. Does the term indicate the family of origin? The family of marriage? In addition, one should indicate cut-off points for relatives. Are brothers and sisters in a twelve-sibling family necessary to family therapy? Kellam, in studying childhood characteristics predictive of drug use in adolescence, identifies over 80 variants of family structures. In the Rounsaville study, subjects recruited for the study constituted less than 5 percent of the clinical population at any one time. In the Woody study over one-third of potential subjects did not make it through the initial three interviews basic to selection for the study. Recruitment in the Stanton study was not random.

What does this lack of generalizability mean for NIDA's research agenda? If we can't generalize from the best studies in the field, why continue to invest in this kind of research? My answer to this question is that it is worthwhile to learn that some addicts profit from family therapy, cognitive, behavioral, or emotional expressive therapy. We can't say that these treatments are applicable to all addicts because of the attrition problem which precludes generalization. But our judgments rest on scientific process which permits us to know the limits of our data base. The author's historical perspective is important here. Building a body of knowledge should rest on the results of systematic observation, and the state of the art, at this time, precludes generalization. This does not invalidate the fact that we have learned that procedure x, y, or z is applicable to some addicts, and we know this on the basis of scientific process.

In the discussion of psychotherapy research in methadone maintenance patients, the author does not mention staff bias as an important variable to be controlled (in other

sections of the paper, she does recognize the importance of this variable). In my experience, paraprofessional staff who frequently define the treatment milieu are strongly biased against professional therapists and professional therapies. Their bias must be accounted for in research designs attempting to learn about clinical services in methadone programs.

I do not concur with the apparent firmness of the author's rejection of relaxation therapies. While the data do not support the widespread application of these procedures, the attrition problem again precludes generalization for or against these methods. They appear to have some benefit for some patients, and I believe that we should continue to explore these techniques.

The author's review of vocational rehabilitation is most important, and I concur strongly with the statement, "Vocational rehabilitation has an important place in methadone treatment, especially to clients." If there is one area in which a modest investment of resources might have the potential of substantial payoff for clinical services, it would be this one. Studies of the effects of training all personnel involved in these clinics in educational and vocational rehabilitation have top priority. In my opinion, clients want this, use it, and, as Dr. Hall's review indicates, appear to benefit from it.

The author's review does not touch on the common clinical problem of abuse of substances other than opioids in methadone patients. Alcoholism services, either offered directly by the program or by referral, are integral to any minimally functioning program. But we have little research on this problem. In my opinion, comprehensive services for all kinds of substance abuse problems, including nicotine dependence, should be offered by treatment programs. All behaviors which adversely affect health should be focused on in treatment. The growing body of data indicating that treatment of substance abuse problems is economical, in terms of preventing future use of standard medical services, is germane to this point.

The author does not discuss fully the role of psychiatric involvement in methadone programs. A growing body of data on psychopathology of opioid dependent persons indicates that high rates of psychiatric diagnoses exist in these populations. Studies in a number of centers indicate that addicts have higher rates of diagnoses of antisocial personality disorders, depressive disorders, minor mood

disorders, and phobic states than exist in community samples. The significance of these findings is well discussed by Rounsaville et al. Further research on psychiatric status is strongly indicated, for it represents a potential for discovering possible treatable illnesses. While it is true that classical psychiatric methods do not appear to be effective with personality disorders, it is also a matter of common clinical experience that they do seem to be helped by the affiliative treatment forms developed to treat addiction. Therapeutic communities and methadone maintenance programs both have had some success treating with these disorders. It may well be that some combination of classical methods with the affiliative techniques we have developed in 15 years could be effective with these problems.

The depression seen in both opioid dependent and alcohol dependent populations seems to be a variant which differs from the kind of depression seen in psychiatric wards, in ways we don't yet understand. Probably this is so because depressive disorders in our patients are importantly produced by pharmacologic factors. The high rates of depressive complaints and depressive syndromes observed in substance abusing populations deserve high priority in NIDA's research agenda. I do not agree with the author's comments on the nonsignificance of personality changes during methadone treatment. We should study these changes thoroughly because they may give us a key to understanding how treatment affects patients.

What do I see as the priorities for NIDA's research agenda for the future? The first priority would be the examination of the role of vocational and educational services for methadone clients. As noted above, this area has the promise of delivering the biggest bang for the buck. The next priority I see is the continuing examination of the psychiatric status of methadone clients together with the systematic attempts to treat the conditions that are detected. As noted above, I believe it possible that the antisocial disorders may be more treatable by us than by anybody to date. The next priority is the continued examination of the provision of comprehensive services for all substance abuse behaviors. The data indicating that a dollar spent on treating drug and alcohol programs saves two or three in future utilization of the medical care system are extremely important from an economic as well as a humanitarian point of view.

CHAPTER 4. PROGRAM POLICIES AND PROCEDURES ASSOCIATED WITH TREATMENT OUTCOME

Christopher D'Amanda, M.D.

INTRODUCTION

Methadone treatment programs now span orientations from broad goals of social rehabilitation to more limited concerns with treating physical dependency (Goldstein and Judson 1973; Nurco et al. 1981a, b, c). Vincent Dole had provided an inclusive model, attending to societal wants by supporting individual needs, but it became polarized over the decade 1970-1980 so that program goals tended to focus around either social or medical goals. Program directors and enthusiasts of each model became zealots for their particular approach, leading to considerable friction, a comparable loss in clarity of purpose, and goal displacement. Program type became more important than client status and the conditions affecting their lives. Solutions gained more political value than the problems for which these solutions were created in the first place. Researchers in the field were also diverted, seduced more by style of service delivery than the substance of what was delivered. Evaluation of program efficacy was (and is) generally limited to statements about different client populations. Replication of these efforts within a given geographic area is uncommon and even more rare between cities or across geographic regions. It is not easy to find contributions from this large body of literature suitable for policy decisionmaking, nor is it easy to find references to policy(ies) which sustain(s) the myriad functions carried out in methadone programs.

In this paper, policy is defined as a written statement which sets standards for action and for the outcomes of such action. The scope of policy may be carried beyond a single program to include decentralized clinics; it may also guide activities down an extensive governmental chain of offices, bureaus, and agencies. "Policy does nothing without the aid of administration; but administration is not therefore politics" (Altshuler 1968). Policy is seen to be the result of a political process whereas administration is a "field of business" concerned with implementing a plan of action, designed to meet policy standards and defined by regulations and protocols. Policy is (in

theory) pro-active because procedural activities administrating change from some former status flow from it. More often, in the real world, policy emerges after administrative order to create a new procedure, remains unwritten, and is identified only by inference. This "policy by deduction" is reactive and permits as many interpretations as there are analysts. In this review we investigate how policy affects outcome by keeping a sharp separation of policy from procedure, or as above, from the field of business called administration.

At the level of local program activity, the National Institute on Drug Abuse (NIDA), the Food and Drug Administration (FDA), and the Drug Enforcement Administration (DEA) are identified as prime movers in local program policy. In fact, none of these agencies has published policy statements for methadone programs, but they are, even so, prime movers in program behavior. NIDA has provided guidelines for service delivery, FDA establishes the protocol for program operation, and DEA establishes regulations for the security of methadone when used for treatment. These documents serve to direct methadone program directors in procedures which they employ to provide client service: these documents assist in the "field of business" called administration.

The impact of the FDA protocol and DEA regulations on local methadone programs has been described as a function of the Federal government's effort "to insist on its jurisdiction" over a new area of service delivery (Attewell and Gerstein 1979). Invoking Thompson's open-system theory of organization (Thompson 1967), the authors show community program vulnerability to these Federal actions. Local program administrators come to elaborate displaced goals (more concerned with survival and less concerned with community impact) because of dependency on central control, i.e., Federal funding. While not disputing the direction of their argument, it contains a common confusion of terminology. Attewell and Gerstein refer frequently to the "FDA protocol" and "other provisions" they later identify as "policy itself." Their paper explores why governmental agencies' priorities often can acquire considerable force even though they are not embodied in law, and therefore encourage treatment programs "to stick closely to the model protocol." The paper confounds procedure with policy and thus blurs their important and separate implications.

Frequent reference will be made in this paper to the SAODAP Manual for methadone treatment published in 1974. It contains considerable direction for local program policy development and stands in some contrast to implications of FDA and DEA documents. SAODAP (NIDA) maintains consistency with medical and social models of heroin addiction, whereas FDA and DEA seem less concerned with issues of addiction, and more concerned with control and law enforcement.

My intent is to look at the literature of drug abuse treatment and methadone maintenance for two things: (1) specific reference to policy statements, and (2) data which has policy implications. The assumption is made that the ideal paradigm for a service program begins with its statement of policy; regulations and procedures are then prepared which support the policy and provide direction for its implementation by staff to achieve delivery of service.

CHOOSING A POLICY POSITION

Reports of policy study in local treatment programs are sparse. Only six authors make reference to policy statements influencing program operations. Jaffe (1970, 1971) encouraged an open admission policy which needed to be balanced by creating a potential for positive treatment outcome to counter community skepticism. Jaffe believed that community support was more likely with a policy directed to encourage social recovery than a policy to deal with biological defect.

Cushman encouraged the acceptance of clients seeking readmission to methadone maintenance, and saw little to support pressures from either the community or government for detoxification. He is consistent with the SAODAP Manual when describing detoxification as a "stage not a goal" of methadone maintenance (Cushman and Dole 1973).

This policy position is supported by Millman, who considered that describing a program as providing maintenance to attain detoxification or abstinence is counterproductive (Millman et al. 1978). Criteria for detoxification have also been described which included the completing of 1 year without drug use and developing positive social changes (Judson et al. 1980). The comprehensive model of methadone maintenance treatment (medical and social services) was promoted in noting the adaptability of patients

continuing to achieve positive outcome when induction to methadone maintenance was shifted from an inpatient to an outpatient setting (Gearing 1970). Lowinson is in agreement with others who state that detoxification should not be considered the goal of treatment. She goes further, however, and describes (a) the value of attempting to discourage early termination, and (b) the importance of being ready to readmit without hassle if the client does elect to detoxify against staff advice (Lowinson and Langrod 1973).

In the following sections we present what information is available regarding policy options for methadone treatment program functions in more detail.

POLICY IN WAITING

Admission

Primary criteria for admission to methadone treatment programs were established by the FDA protocol and consist of a minimum of 18 years of age and 2-year history of opiate addiction. These criteria have not been questioned in the literature reviewed, but a recent change in the period of opiate dependency to a minimum of 1 year reflects response to clinical realities of heroin users. There has been no reflection in the literature on the change in this criterion, or its impact on treatment outcome. Providing for flexibility in the age criterion has apparently been sufficient to respond to the heroin user who is at least 16 years old. The absence of any studies and/or criticism of these admission criteria may represent consensus in the field that they are appropriate, or that field efforts to alter the FDA protocol are ill advised, futile, or both (Attewell and Gerstein 1979). There are no clinical data to suggest that either the age criterion or the 1-year dependency criterion should be adjusted. This is not to say, however, that effort should not be made to discuss additional and/or differing criteria for admission policy. Refinement of admission criteria could be forthcoming from behavioral variables which have been defined in relation to criminality and prostitution (Ball et al. 1980; D'Orban 1975; File et al. 1974; Levy 1972; Nurco et al. 1981a, b, c; Simpson and Savage 1980). These could well lead to a policy of coordination between the treatment and criminal justice systems.

Discharge

Any discussion of policy-related outcomes concerned with a discharge must begin with the fact that many patients entering drug abuse treatment programs leave before completing treatment (Savage and Simpson 1978). While this category of program termination is lowest for those clients entering methadone maintenance, the fact remains that program discharge is only partially in the hands of those responsible for policy development and program administration. The vast majority of studies indicate that length of time in treatment is associated with effective functioning in the community (Simpson et al. 1979a; Simpson 1979; Sells 1979; Cushman 1978; McGlothlin and Anglin 1981a). Some few studies have disagreed (Brown et al. 1972a; Burt et al. 1980; Gorsuch et al. 1976). Of those clients who do not complete treatment, the vast majority elect to quit, while a comparatively small number are expelled.

Treatment assessment can be problematic for the responsible but "trapped administrator" who easily risks "political vulnerability from knowing outcomes" (Campbell 1969). However, the administrator has available options which minimize this risk but require policy decisions. Outcome studies could become the responsibility of regional or State government, working to aggregate individual program data. Study design could recognize the "vanishing sample" by requiring that the entire applicant pool be included as denominator rather than only those who "complete" their treatment plan (Hill 1961). And demystification of methadone as a "magic bullet" could be accomplished sufficiently to permit conceptualizing long-term abstinence as a function more of learned alternatives to addictive behavior than of a particular method employed to interrupt such behavior (Vaillant 1966b). Any one of these considerations leads to viewing discharge policy in terms of a societal problem to be addressed rather than a program modality to be defended.

Readmission

This issue is virtually unaddressed in the literature reviewed. Two reports describe programs in which readmission policy is encouraged (Cushman and Dole 1973; Lowinson and Langrod 1973). One author suggests that readmission should occur "without hassle" even if the client has been terminated against medical advice (Lowinson and Langrod

1973). By inference, and personal experience of the writer, this policy appears rare among methadone maintenance programs. Support for this conclusion is provided by the decision of Sells and his group that readmission should be scored negatively in their determination of outcome for methadone maintenance patients. This decision is predictable given the estimation that evaluation efforts in the field are more oriented to the defensive proposition of program justification than to a more neutral position of assessing impact on the problem of addiction in society. The latter would lead, for instance, to use of a life history questionnaire, whereas the former would be content with assessing time in treatment.

A singular effort to explore the complexity of readmission and its significance to treatment outcome is worth brief mention. The first two Drug Abuse Reporting Program (DARP) cohorts were examined 3 years after DARP treatment, classified in one of eight patterns determined by whether or not no treatment for a given year had been experienced ("N"), or the respondent had participated in any kind of drug treatment program at least 1 month in a given year ("T") (Simpson and Savage 1980a). The most favorable outcome was obtained by 42 percent who were NNN. The most unfavorable outcomes were found for those persons who had been out of DARP treatment at least 1 year before reentering, pattern NTT (9 percent) or pattern NNT (7 percent). Those respondents who had been in treatment each year post-DARP (TTT) represented 27 percent of the sample and had outcomes which fell in between these groups. The greatest positive change from pre-DARP to follow-up was observed for respondents with patterns TNN and TTN.

The practical implication of these data supports the policy positions described by Cushman et al. (1973) and Lowinson et al. (1973). Readmission may have some predictive value for outcome and might be studied by an experimental design which could pursue identification of concomitant variables associated with the several patterns developed by the DARP group. Policy statements concerning readmission need not, however, depend on the outcome of such studies given acceptance of the perspective of addiction as a chronic and potentially relapsing disorder. From the SAODAP Manual, staff are directed to "reinforce the idea that the client is not a failure because he needs this treatment modality" (MTP) when a recidivist applies for intake.

At the very least, a decision to institute a policy supporting readmission could be based on the observation that previous termination from methadone maintenance reflects neither program nor patient failure but a discordance among a variety of variables characterizing the patient and the program (Szapocznik and Ladner 1977), best considered under the concept of "goodness of fit" (Simpson and Savage 1980b).

Detoxification

Policy considerations relevant to detoxification can be more readily approached if the subject is divided into three areas of discussion: (1) the narrow consideration of detoxification from heroin as a distinct service provided within less than 21 days; (2) the place of detoxification in a program providing methadone maintenance; and (3) the process of detoxification from long-term methadone therapy.

Heroin Detoxification. For most workers in the field, detoxification of heroin-dependent persons receives little favor and less program implementation. The lack of enthusiasm has both a clinical and political rationale. The latter requires that treatment programs funded to serve the heroin addict be able to claim that rehabilitation has occurred, and this outcome is manifestly improbable after ambulatory detoxification (Wilson et al. 1975). Such a short-term program can only be justified and relevant policy can only be promoted if the rationale is to provide emergency medical care. From this perspective, it is not unreasonable to argue that the absence of such programs constitutes a degree of "cruel and unusual punishment" or "unequal protection" for the opiate-dependent person by comparison with services readily available for other emergent drug-related conditions including alcoholism.

The clinical rationale also depends on the rehabilitation focus justifying the basis for intervention. Need for lengthy treatment follows from the medical model (addiction as disease). But if this medical model is applied with consistency, then ambulatory detoxification for relief of dependency would be an acceptable if only partial intervention. A discussion of logical consistency is, however, not within the purview of this paper. Ambulatory detoxification can be visualized as accelerating a process through which the heroin addict is known to go repeatedly in the street, and which, for some unknown proportions,

results in (a) the decision to seek rehabilitation in a treatment program, or (b) the decision to become abstinent without benefit of program services.

Four references to heroin detoxification were found, with as many differing conclusions: "methadone maintenance is an effective treatment modality for more heroin addicts than methadone detoxification" but "there is a definite place for detoxification treatment" for those who refuse maintenance or are not eligible for it (Katon et al. 1972); detoxification may serve as a pretreatment phase for maintenance (Chambers et al. 1970b); detoxification can be successfully achieved with cooperation between a community treatment program and a hospital (Jonas et al. 1972), and, detoxification by itself is a popular service with addicts (Werner et al. 1973).

The sole study of detoxification as an emergent service for heroin-dependent persons reports outcomes for over 20,000 persons who entered the New York City Ambulatory Detoxification Program from July 1971 through December 1972. More than half completed the full 7-day cycle of decreasing methadone doses. Of the 34 percent referred to long-term programs, 30 percent were still there 30 days after the referral. The conclusion is persuasive: "It is, perhaps, especially noteworthy that such extraordinarily large numbers of addicts voluntarily sought admission to this program; this certainly suggests that the treatment provided is perceived as beneficial by those it serves" (Werner et al. 1973).

Methadone Detoxification--Place in Maintenance Treatment. The SAODAP Manual provided a cautionary note on detoxification which has not been appreciated in the field: program administrators are urged to set more criteria for treatment termination than merely "completing detoxification (e.g., four weeks clean urine), and all clients who have been detoxified should be encouraged to stay in treatment a specified length of time. Specifically, detoxified clients should be urged to stay in treatment... for a period of approximately three months while urine testing and counselling continue."

How a given methadone maintenance program approaches detoxification after maintenance is a crucial and not often reported consideration. Advertising maintenance programs as permitting or encouraging detoxification has been described as "counter-productive" (Millman et al. 1978).

Detoxification is preferably considered a stage of treatment (Cushman and Dole 1973; Kleber 1977; Lowinson and Langrod 1973), even though practical considerations may tend to defeat this policy within a maintenance program. Newly abstinent clients may be highly resistant to continue treatment with their still dependent peers. A strong statement of policy to support social as well as medical goals is necessary to overcome client resistance and reinforce staff commitment.

The evolution in attitude about outcome after detoxification by one careful worker in the field is instructive. In the early 1970s Cushman (1974) indicated that a "substantial fraction" of maintained patients had successful outcomes. After further follow-up of this patient population he observed that "the detoxified patient is not necessarily further rehabilitated or even better off." After 11 years of observation he concluded that detoxification is only "good for a small minority" estimated to be approximately 1 percent per year of patients in a methadone program (Cushman 1978b).

Stimmel is in substantial agreement with this sentiment, reporting a 6-year study (which includes a followup period averaging 30 months) of formerly methadone-maintained patients: 35 percent were narcotic free and 65 percent had returned to heroin use (Stimmel et al. 1977). He cautioned against the "impressive risk" of returning to heroin use sustained by those clients who left before program completion occurred (Gardner 1980).

Methadone Detoxification--Process in Methadone Treatment. The observation made in 1977 that there is no consensus and little data to permit a clear understanding of detoxification still seems appropriate (Kleber 1977). Kleber identifies six areas which need careful description to properly understand outcomes after detoxification: selection criteria, rate of withdrawal in relation to the dose at which the client had been maintained, blind versus open detoxification, ancillary supports, supplemental methadone or other medication, and use of experimental techniques. A description of program policy about the use of methadone should also be included as a seventh area to be covered: adherence to the unadulterated medical model by program staff could well lead clients to be victims of a self-fulfilling prophecy resulting in return to heroin, once, for whatever reason, they elected or were required to terminate methadone maintenance. The possibility of such an outcome is a clear reflection of the power program policy

(most commonly in this instance, policy by deduction) can have on treatment success.

The use of placebo medication would be a worthy addition to Kleber's six areas of experimental techniques. Despite the author's impression from personal communications that this is not an uncommon practice, only one mention of placebo use is found in the literature reviewed. A decade ago Cushman and Dole stated that placebo therapy was not useful in methadone-maintained patients undergoing detoxification (Cushman and Dole 1973).

The study by Chappel et al. (1973) remains the single large-scale evaluation of outcome for groups of methadone-maintained clients undergoing three detoxification regimes compared with a group attempting "nontherapeutic" withdrawal against the advice of clinic staff (Group I). The highest rate of completion was observed with clients who received group therapy (Group III), followed by those clients for whom support was provided within the unit for detoxification (Group II), followed by clients who underwent detoxification in a residential facility (Group IV). This order of group outcomes in relation to completion rate was, however, not maintained when other outcomes were measured. Thus Group IV was best in achieving abstinence while in treatment, and members of Group II were found to return most frequently to methadone therapy.

In summary, it seems essential that programs providing methadone beyond 21 days call themselves maintenance programs and that research efforts to analyze differential outcomes among detoxified patients be careful to describe both significance given to and process of detoxification. A detoxification policy can only follow a clear-cut statement of program policy which declares its purpose in providing methadone maintenance in the first place. Finally, clinical and political questions of outcome must specify what particular outcome is being targeted.

Urine Testing

Considering the amount of energy and time devoted by treatment staff and their clients to discussing the when, where, and how of urine testing , and what meaning is attached to results of urine testing, it is extraordinary that there is but a handful of reports to be found. The observation remains almost as true now as when it was made in 1977 that there is no answer to "whether or not urine

testing per se has any value" (Goldstein et al. 1977). Multiple questions remain unanswered which relate to policy on the matter. Is the client observed, and by whom? Are results discussed, ignored, or do they contribute to disciplinary action? Are split samples or other methods employed to detect lab error? The silence in these areas is sufficiently surprising to suggest some form of collective guilt among providers over the demand that a client can only "buy" access to methadone after making a urine sample "deposit."

One exceptional paper reports results from a year's observation of nonmonitored (by urine surveillance) and monitored (routine surveillance following State and Federal requirements) clients in five different methadone treatment programs in California. Havassy and Hall conclude that "results...do not indicate that urine monitoring is a strong uniform deterrent to illicit drug use. They also do not indicate any deterrent value for any particular subgroup of clients, such as younger or older clients; those new to treatment or treatment 'veterans'; men or women" (Havassy and Hall 1981). Further cautionary inferences come from low levels of accuracy in routine laboratory reports of urine submitted for drug analysis (Gottheil et al. 1976). Gottheil encourages better awareness among staff of fallibility in test results and consideration at the Federal level of changing the requirements for urine surveillance. The latest FDA protocol does, in fact, move significantly in this direction. It states that a urine positive for narcotics is "not a requirement for admission to detoxification or maintenance treatment" and that only eight further studies are recommended during the first year of maintenance. Medical staff are now concerned that no third party billing is available if more complete monitoring is in order, and reimbursement programs accept these minimum recommended procedures as preferred policy. This is only one example of how confusion about procedure and policy adversely affects service delivery and may alter outcome.

The use of urine testing in follow-up studies is generally considered to have limited value because of the rapid decay of most drugs vis-a-vis the intent of such studies to gather history over a long period of time (Stephens and Cottrell 1972). Urine testing would also add considerably to the cost of these studies. More importantly, a growing body of reports concerned with addict self-reporting strongly supports the reliability and validity of this

methodology, given attention to certain details of technique (Amsel et al. 1976; Ball 1967; Ben-Yehuda 1980; Bonito et al. 1976; Simpson et al. 1976).

Dosage

While there has been a generally downward trend in the milligrams of methadone prescribed to patients in maintenance treatment programs over the previous decade, the selection of dosage still results from a combination of the program's personal preference--less or more is better--and the choice of the pharmacologic rationale for its use in the first place. Jaffe dichotomized this latter question to the decision of whether methadone controlled narcotic hunger (craving), for which low dose was sufficient, or whether it was necessary to achieve cross-tolerance (blockade), for which high dose was used (Jaffe 1971).

Reports from Chicago were the first to articulate the possibility that a psychological or social model was operating in the continued dependency on heroin described as addiction, rather than the classic biological model which postulated a defect, or at best an alteration, in the body's metabolism which once present was unlikely to be removed. The resulting controversy about the merits of either low- or high-dose methadone in some ways served to displace the debate of methadone or no methadone and remains, in policy terms, at impasse.

Clinicians seem, generally, to take a prudent position that less is better, and choose with greater willingness (now) to be empirical, seeking a dose schedule which supports maximal functioning of the individual client. The inclination is strong, however, to follow Goldstein's lead and use doses under 50 mg (Goldstein and Judson 1973). There is some clinical sense that the hardcore "classic junkie" will be more effectively treated with higher doses and that the newer or generally younger recruit to heroin can be maintained on lower doses. There have been no policy statements, however, to this effect and there remain no policy statements to support whatever dosage is selected. The difficulty here more than likely derives from the lack of closure on the original question posed by Jaffe, which had as much to do with the mechanism of addiction as it did with understanding the pharmacologic action of methadone.

Certain outcome characteristics associated with dose regimen have been identified. High dose was associated with a more rapid decrease in heroin use than low dose, and high dose seemed to be associated with increased retention whereas low dose carried with it the possibility of increased incidence of depression, dropout rate, and more persistent if not greater use of heroin (Chambers and Taylor 1973; Siassi et al. 1977; Siassi et al. 1972). A more detailed analysis of the effects of methadone dose and duration is performed in a previous chapter by Dr. Hargreaves (part I, chapter 2).

The concept of self-medication as a motivation to maintain dependency has received increasing currency. This formulation represents a swing of the pendulum toward a middle ground from the position of moral indignation which inclines to "blame the victim." Low dose methadone has even been suggested to be risky because it may "fail to sufficiently suppress the patient's strong aggressive disposition" (Chambers and Taylor 1973).

A few studies have looked to the clients themselves to see what preferences might exist for high or low dose and/or dose control. Client interest in dose control was third after choices of a stipend or maximum take-home privileges (Stitzer and Bigelow 1978). Contingency management of dose control may serve predictive purposes (Stitzer et al. 1979), but conditions in the community, e.g., waiting lists for admissions, were noted to diminish the utility of this approach to treatment.

Studies published in 1981 from work by McGlothlin and Anglin are most helpful in providing a corrective movement to the inclination that "less is better." Their work points clearly to the value of higher blockade level doses of methadone for attaining the usual outcome criteria and, most importantly, in terms of cost effectiveness (McGlothlin and Anglin 1981a; McGlothlin and Anglin 1981b).

Take-Home Doses

It is remarkable, as with urine testing, that a program procedure which occupies so much staff and client energy has received virtually no discussion in the literature. One looks in vain, for instance, for reports of during-treatment outcomes associated with two take-home vs three take-home medication doses.

A plausible explanation for this silence can be inferred from language in the NIDA Manual. While no direction is given for a clinic to operate 7 days a week or that a client must receive methadone on program premises 7 days a week, no other interpretation seems warranted from the statement that "after 3 months in treatment...the clinic may allow him the privilege of take-home medication." The latest FDA protocol both ignores and overcomes any problems of interpretation by stating that "a patient be under observation while ingesting the drug daily or at least 6 days a week, for at least the first 3 months." The predictable result is that take-home methadone is provided in the first week of treatment and the utility of take-homes as earned through responsible behavior is seriously undercut. The paucity of studies, then, is another instance of sensible avoidance of the "vulnerability of knowing outcomes."

Take-homes, as behavioral modifiers, were not found to be a useful reinforcer in one study (Havassy et al. 1979), but were helpful in another to achieve standard outcomes in spite of the risk of increased diversion (Milby et al. 1978). Take-homes were valued over other opportunities of contingency management in a questionnaire survey of maintenance patients (Stitzer and Bigelow 1978). The reality of economic survivorship for most heroin users renders the results of these studies highly questionable in an outpatient setting.

The clearest implications for policy makers interested in take-home medication comes in a report from Boston which describes the effect of a political imperative requiring the institution of a no take-home policy or the loss of all funding to support methadone maintenance (Patch et al. 1973). For 3 months after the changeover from traditional take-home privileges, discharge and readmission rates increased but then returned to baseline or slightly less than baseline levels. No deterioration occurred in client outcome for those remaining in treatment for a year after the new policy was in effect. A significant number of clients were able to obtain employment and/or maintain their jobs while on a 7-day pick-up schedule. The rate of clients seeking detoxification was also unchanged.

These results were taken to represent some contradiction to Dole's statement that providing no take-home privileges is "disastrously mistaken." Credit must be given to the opiate-dependent person's adaptability at the least, and

to his or her potential for superior motivation at the best.

Alcohol Use

Problems among methadone-maintained patients with the use of alcohol have been reported infrequently over the past decade. More recent data indicate that alcohol use has significant rates of prevalence and incidence in this population. Material to follow suggests that concern with alcohol use among methadone clients is already past due and is affecting outcome in manifold, unstudied ways.

The statement voiced in 1976 in the earliest paper looking with some detail at the matter is challenging and important: "Alcohol consumption may present a greater threat to successful rehabilitative outcome then continued use of opiates" (Riordan et al. 1976). "Manifest alcoholism" was reported in 15 percent of 68 detoxified patients, 23 percent of whom (three of 13) developed this condition "during and after detoxification" (Cushman 1978b, emphasis added). The condition seemed independent of opiate use per se, in that eight alcoholics were in the narcotic free outcome group (of 36), and five were in the relapse group (of 32). An increase in alcohol abuse following entry to methadone treatment is also noted by McGlothlin and Anglin 1981a; 1977).

Another study concluded that "in general, after a client enters treatment his (or her) drinking patterns will sharply decrease," but this does not follow from the study data (Ginzburg 1977). The percentage of clients consuming less than 0.5 ounce of alcohol before and during treatment decreases in four modalities, but for methadone maintenance the percent increases from 33 percent to 39 percent; further data from the methadone population included the fact that 67 percent of the pretreatment population were nondrinkers, and 33 percent were drinkers. During an average 2-month period in treatment, 61 percent were nondrinkers and 39 percent were drinkers; interviewed 4 years after treatment, 5 percent reported alcohol problems 2 months before the follow-up interview. Data from another large study compare drinking habits 1 year before treatment and 1 year before follow-up (5 years after the first dose of methadone). Daily drinkers increased 48 percent; 25 percent reported being heavy drinkers during and after their treatment. The authors offer the sanguine conclusion that "it is not surprising that our data show some

increase in alcohol use at followup because of the generally held view that alcohol use varies inversely with narcotic use and a marked decrease was found in daily use of heroin" (Judson et al. 1980).

Simpson observes in his highlights from DARP cohort data that "results for alcohol use and employment indicate mainly that rehabilitation of clients in drug abuse treatment requires more focus of resources in these areas than the treatment programs were generally funded to obtain" (Simpson and Sells 1981). I would add that resource allocation in the past should not preclude policy considerations for allocation in the future.

Pre-DARP, the percent of methadone maintenance heavy drinkers was not greatly different from that noted in other modalities (table 1A and 1B). During treatment, however, only one-third of heavy drinking methadone maintenance clients stopped, contrasted with two-thirds to three-quarters of heavy drinking clients who stopped during treatment in other modalities. Drinking at some level was maintained by 62 percent of methadone maintenance heavy drinkers (total figures in three right-hand columns of table 1A, while only 11 percent to 32 percent of heavy drinkers continued after entering other modalities. Table 1B records onset of drinking during treatment by clients abstinent prior to intake. Thirty-one percent of such clients entering methadone maintenance began alcohol consumption. In other modalities this behavior occurred only among 5 to 12 percent of the clients.

Table 2 is another composite of DARP data of contrasting use of heroin, marijuana, and alcohol by the three DARP cohorts. Three distinct patterns are present: marijuana use is biphasic, with peak consumption during treatment; heroin use is linear, following a dramatic decline from the pre-DARP baseline; alcohol use is also linear, but shows a progressive increase from baseline values, continuing upward during treatment to peak at the follow-up interview.

The writer proposes that there is sufficient information available to require consideration of alcohol use among methadone-maintained patients as a priority policy concern.

The need for careful thought on the matter is apparent from the single large-scale study, coordinated by Eagleville Hospital and Rehabilitation Center, that looks

Table 1. Heavy Alcohol Use and Abstinence Before and During DARP Treatment by Modality*

A

	Percent total patients in modality consuming >8 oz/day pre-DARP	Percent patients by average ounces total alcohol consumed/day during DARP			
		0	1-4	4-8	>8
Methadone maintenance	14%	38%	29%	22%	11%
Therapeutic community	19%	89%	7%	2%	2%
Drug free	15%	68%	13%	6%	13%
Detoxification inpatient	15%	87%	3%	3%	7%
Detoxification outpatient	11%	70%	9%	6%	15%

B

	Percent total patients in modality consuming 0 oz/day pre-DARP	Percent patients by average ounces total alcohol consumed/day during DARP			
		0	1-4	4-8	>8
Methadone maintenance	67%	69%	22%	7%	2%
Therapeutic community	66%	95%	4%	1%	0
Drug free	61%	88%	9%	2%	1%
Detoxification inpatient	73%	95%	1%	2%	2%
Detoxification outpatient	73%	89%	6%	3%	2%

*Data from Table 2.12 (N=24,126 in Cohorts 1, 2, 3) p. 53, Data Book on Drug Treatment Outcomes (Simpson et al. 1978).

Table 2. Alcohol, heroin and marijuana use before and after DARP*

	Baseline	Percent during 3 years after DARP	Percent during last year before followup interview
Heroin			
Daily use	68%	39%	16%
Any use	81%	58%	30%
Marijuana			
Daily use	15%	26%	23%
Any use	52%	67%	62%
Alcohol			
Over 4 oz.	21%	32%	33%
Over 8 oz.	13%	17%	19%

*Data from Tables 2 and 7 (N=4,627 in Cohorts 1, 2 and 3) pp. 13, 40, Highlights of DARP Follow-Up Research (Simpson and Sells 1981).

at levels of alcohol use and problems associated with alcohol among heroin addicts (Gardner 1980). Here, the question of whether methadone maintenance led to alcohol abuse was answered, "This is not generally the case: Those who remained on methadone maintenance the entire year were no more likely to have a drinking problem on followup than were those who received methadone for a shorter time." Nonetheless, an "appreciable" minority of some 18 percent who claimed abstinence at intake did report excessive drinking at follow-up.

Interestingly, "heavy drinking at the time of followup was not associated with poor outcome in aspects of functioning other than alcohol use and abuse while pretreatment heavy drinking did predict poor treatment outcome. Overall, it was found that 50 percent of the drug addicts in this study sample had consumed excessive quantities of alcohol at some time in their lives, and 25 percent reported that they had experienced a significant number of alcohol-related problems, i.e., symptoms of alcoholism." Implications for management of these patients were clearly

stated: "Those with a history of problem drinking... reported significantly more pathological histories than did other subjects...and their drug use was based more on psychological needs than was the case with other addicts" (Gardner 1980). Alcohol use, whether continued, accelerated, diminished, or newly initiated is part of the clinical picture for heroin addicts in methadone maintenance treatment and should be part of any methadone program concern.

Women

"Little is known about the forces which combine to produce a female addict, and what little there is has been extrapolated from research on male addicts, as a model of female addiction has not yet been developed. Most programs operate from the perspective of male-oriented treatment models, which are inappropriate to the needs and problems of female addicts, and which probably discourage a significant proportion from entering treatment" (Cuskey et al. 1977). For those few women in terms of estimated need who do decide to enter treatment, they appear "with a range of needs that programs are unwilling to identify and/or treat" (Cuskey et al. 1977). It seems a small stretch of the imagination to anticipate that these conditions will produce a significant effect on outcome of women in treatment and will require appropriate policy decisionmaking to establish a more sensible and sensitive approach.

Major reviews (Burt et al. 1979; Cuskey et al. 1977; Cuskey et al. 1972) and a single, well ordered, and extensive cooperative study coordinated from Detroit, the National Women's Research Coordination Project, have illuminated glaring problems in equitable service to female users of opiates and other drugs. While these reports have raised our general level of consciousness somewhat, it is probably fair to say that treatment programs in general and methadone maintenance programs in particular have not responded to the issues of providing appropriate treatment to women clients.

Women's presence is only minimally observed in reports of methadone maintenance treatment. Eighteen percent of the articles reviewed described treatment populations by sex but did not further analyze outcome variables by sex. Outcome variables were analyzed by sex in only 8 percent of the articles. This lack of attention to particular

outcomes for women is not limited to authors of the opposite sex.

A very small group of workers have looked at particular attributes of women heroin users, reporting data of significance for program operation and policy far outweighing their small numbers. Finnegan describes women's unique pharmacodynamics for certain drugs, interactions with oral contraceptives, and altered effects during pregnancy (Finnegan 1979). Impact of prescription drug use by the pregnant woman has been found to have more complex effects on the fetus, "always an unintended recipient" of drugs taken by the mother, than were observed in earlier years among pregnant heroin using women. In a survey of middle to high socioeconomic pregnant females, 55 percent reported self-medication: subjects used an average of four prescription drugs; 64 percent of these were nonnarcotic analgesics, 24 percent were sedatives, and 5 percent were narcotics (Finnegan 1979).

Little information on sexuality among drug addicts is available and that which is "overwhelmingly pertains to men" (Wasnick et al. 1980). The results of a study conducted recently in Philadelphia are instructive. Forty-six percent of the interview sample of 50 women heroin users entering the Central Medical Intake in search of treatment reported having been raped or forced to commit a deviant sexual act; 28 percent reported sexual abuse as children; 84 percent reported sexual dysfunction as adults, the majority listing multiple problems. Of those women who had had previous drug treatment experience, 86 percent reported that a discussion of sexuality and/or sexual assaults was never initiated during treatment. Thirty-nine percent of this group reported, in fact, that they had been sexually harassed by treatment program counselors or other staff (Wasnick et al. 1980). It seems apparent that if clinicians in the treatment system wish to provide appropriate service to women heroin users they must ask more pertinent questions both of their clients and of themselves.

Criminal Behavior

From a collection of four dozen papers concerned with criminality, heroin addiction and outcome, the following were selected because they provide opportunities for policy discussion. Ball defines a new measure of criminal behavior which he called crime-days per year at risk, and

was able to demonstrate that "it is opiate use itself which is the principal cause of high crime rates among addicts. Once addiction ceases, crime rates drop markedly, and this notable decrease in criminality (an overall 84 percent decline) occurs for all types of offenders throughout the risk years. It is apparent, then, that a major means of reducing the amount of crime committed by opiate addicts is within sight. If we can control addiction, it is evident that we will reduce criminality appreciably...we know that criminality is rampant among heroin addicts. We know that addiction markedly increases criminality. And, we know that addiction can be impacted through treatment and control measures" (Ball et al. 1981, emphasis added).

The framework for further study of criminal behavior by the heroin addict is provided by Nurco, principal investigator of the Baltimore study, who produced a new typology defining addict careers. Type 1 and Type 5 addicts are most in control of their destiny. Either through voluntary abstinence or staying heavily involved with narcotics but successfully avoiding incarceration, they "demonstrated the most social competence by maintaining greater preaddiction job stability then their addict peers." Nurco also reports that the "structure of narcotic addiction for black addicts is quite different than it is for many white addicts" (Nurco et al. 1981a). In Types 1 and 3, for instance, one-third of the white addicts never regarded heroin as their dominant drug. Further, it is noted that while illegal income is the principal source of economic support during periods of addiction, white addicts in Type 1 are distinguished by being more likely than members in any other group to derive the bulk of their income from employment, family, and welfare (Nurco et al. 1981b). Across a 25-year period of observation little change is noted within racial groups of their background variables, although differences were observed between them. Whites were noted to display an increased pattern of addiction occurring less than 50 percent of the time and incarceration occurring most of the remaining time. For both racial groups an upward trend was noted in preaddiction crime (Nurco et al. 1981c).

Implications for service delivery within the field are many, including a significant improvement in refining outcome variables in relation to the typology presented. Nurco defines two policy options available: one, the classification in the criminal justice system of Type 2 and Type 4 addicts at their first prison sentence with

referral to treatment; and the other, to implement early intervention at juvenile court where most white Type 1 addicts are found.

CONCLUSION

We can provide a qualified yes to the question of whether policy, as we define it, has been reported to affect outcome. Only limited, local examples exist and significant questions remain of differential impact (outcomes) related to different policy statements. Therefore, the possibility of choosing one policy as better than another is not now available. Are terminated clients, including those who "graduate," better off or worse off in Chicago (social model) than in New York (medical model)? Are they better or worse off in Boston, and now Washington, with no take-home privilege, or in other cities and programs where this privilege is available? Are they better or worse off in programs which consider detoxification a "step" or in programs where it is a "goal"? Are they better or worse off in programs in which readmission is considered part of the addiction cycle or those in which readmission represents failure? Choice of policy must currently remain bound to local issues without benefit of comparative outcomes from differing sites clearly identified with documented policy statements. Too often, seeking an answer to whether policy affects outcome requires a determination of policy by deduction. Too often, when policy is published, it is relevant for only one of the myriad functions of treatment program responsibility. Careful review of data already on hand, and careful planning to elaborate field specific research designs which capture data not now available should establish rational foundation for policy statements. The design will need to separate measures of output, i.e., actual staff effort, from measures of outcome (client results); outcome measures, no matter how broadly defined, are insufficient by themselves.

Is it possible to relate policy to outcome now? Discharge policies affect outcome so diversely as to make differential evaluation (by program type, regions, etc.) impossible. Discharge categories are described in the SAODAP (NIDA) Manual, and criteria could be elaborated for them to permit an outcome study, preferably undertaken to protect local program vulnerability. Readmission policy undoubtedly affects outcome but no data are available to say how. The writer is sympathetic to Cushman and Lowinson's position that readmission be anticipated and completed

without fuss. They do not report improved results for these clients, however, so we cannot know how outcome may be affected by this sensible policy.

Detoxification should be defined by those who wish to write about it. Continuing to deny service for detoxification from heroin maintains a tradition of second-class citizenship and unequal protection for the heroin user. Kleber's six points are an excellent start, with additional attention given to describing detoxification either as a goal of treament, a process within some broader treatment goal(s), or some combination of each. Cushman's estimate for maintained patients who can be successfully detoxified remains until equally careful work is performed again. The work by Chappel is instructive for programs which seek to devise a policy which is directed to a particular beneficial outcome. Placebo use should be documented, its utility demonstrated, or its practice discontinued--unless Cushman and Dole's dictum of 1973 is accepted and such steps are considered unnecessary.

Urine testing policies clearly exist, but cannot be demonstrated to have an outcome effect on illicit drug use. Havassy and Hall's excellent study seems unequivocal in documenting this conclusion. This study is important in large measure because of the careful attention to developing a field specific research design. Urine testing is not without its utility but improved outcome in terms of heroin use is not among its benefits.

Dosage levels for patients maintained on methadone have been vigorously debated along a full spectrum of perspectives from rhetorical to pharmacodynamic. That dosage policy affects outcome is incontrovertible but opinion varies on how and why. McGlothlin's work, another example of field specific research, provides excellent support for a policy decision favoring higher methadone dosage.

Take-home medication apparently does not affect outcome in terms of treatment retention. An outcome study comparing programing in Boston and Washington with programing in other cities where take-homes are provided is necessary to reveal if other differential outcomes are present.

Use of alcohol by clients in methadone treatment requires urgent and careful study. The seriousness of this still poorly described phenomenon warrants attention at local and national levels. Alcohol use must affect outcome of

methadone treatment clients. Its use deserves more consideration than the usual program injunctions against consuming intoxicating chemical substances.

Alcohol is unique among chemical substances of abuse because it serves as both a substitute and a replacement to heroin. Other drugs are substituted rarely, if ever, for readily available heroin and are routinely considered poor alternatives. The DARP material implicates a particular vulnerability of methadone maintenance clients to alcohol abuse. Policy about use of alcohol is both appropriate and necessary to provide for realistic outcome measures and to permit better understanding of the important variables involved.

No formal policy statements deny women access to methadone treatment programs, except, in some instances, when they are pregnant. Women receive a clear message, nevertheless, from program and system operation which is effectively discriminatory. Services are not available to assist women; staff attitudes and behaviors are not conducive to their being welcomed or afforded respect. Basic information, such as that available in numerous publications by Finnegan, is not utilized. The sexuality issues studied by Wasnick are rarely mentioned. Unwritten policy (in this instance) has a significant and negative effect on outcome as determined by the underrepresentation of women heroin users in treatment and their apparent excess failure rate.

Treatment programs have more or less comfort working with the criminal justice system and persons under its jurisdiction. The implication of Ball and Nurco's work in Baltimore provides a strong rationale for policy which supports collaboration between local treatment and local law enforcement agencies. Ball's analysis of crime days during exposure to risk of heroin use is a challenge to any treatment program, feeding directly into the relationship of individual and societal well being and the pivotal role methadone programs can play in that relationship. The implication for society in the crime day data is a criminal justice system analogue to Dole and Nyswander's medical model: societal well being and the individual heroin user's well being is served by methadone maintenance treatment programs.

The most important development which could improve our knowledge about whether and how program policy(ies) affect client outcome is clarification of the separate meanings

for administration and policy. The first is carried forward through regulations, procedures, and protocols; the second is the result of a political process and sets standards for implementation efforts. When policy is reported--and not confused with other "provisions"--then established goals can be tested and found to meet individual and societal expectations, or not to do so. The link between policy and outcome may be understood and change initiated so that one truly supports the other for better individual and community health.

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CHAPTER 5. COMMUNITY CHARACTERISTICS ASSOCIATED WITH TREATMENT OUTCOME

J. David Hawkins, Ph.D.

INTRODUCTION

The term "drug abuse treatment" is, in a sense, a misnomer. With the possible exception of withdrawal services, drug abuse treatment is a response to a phenomenon much more comprehensive than the misuse of psychoactive drugs. The original goal of the pioneering work of Drs. Dole and Nyswander in developing a methadone maintenance approach to treating heroin addicts was to provide a stabilizing clinical situation to allow "heroin-dependent people to think through their problems in finding work, to achieve reasonable and significant relationships with others, to gain a measure of confidence in their capacity to manage their inner state, and to get on better in society" (Liaison Task Panel 1978; see also Dole et al. 1968). Drug abuse treatment programs do not seek merely to stop the illicit use of drugs, but rather to assist people who no longer are functioning effectively in legitimate society, whether personally, socially, or economically, to adopt different patterns of living (Drug Abuse Council 1980). It has been widely recognized that social rehabilitation services are essential to the successful treatment of drug abusing clients (Bloom and Sudderth 1971; Lewis and Sessler 1980). If treatment is to be effective in realizing the broader goal of social rehabilitation, it must address the social factors related to the initiation, maintenance, and return to drug abuse.

A great deal of research has focused on social factors in the etiology of drug use, and social functioning has been included as an outcome measure in drug treatment program evaluations. However, a promising area of study relevant to an understanding of how former drug abusers can be assisted to function better in society has been largely ignored by both social scientists and medical researchers. That is the ecological study of drug abuse and drug abuse treatment. Most medical and psychological researchers have focused on the individual client, his characteristics, and treatment experiences as predictive of treatment outcomes. Studies in this vein have attempted to identify the characteristics of individuals most suitable

for treatment (see the reviews by McLellan and Woody in this volume, part III, chapters 1 and 2). Typically, social psychologists, sociologists, and social work researchers have broadened the field of inquiry only slightly to include relationships with immediate family members and best friends, and consideration of sociodemographic characteristics of the individual (see the review by McLellan in this volume, part III, chapter 1).

With rare exceptions such as the Hughes et al. (1971, 1974) studies of heroin copping areas in Chicago, the larger social environment, specifically the community context in which individuals initiate, maintain, discontinue, and return to drug abuse, has not been studied. Studies of the effects of this community context on drug treatment outcomes are rarer, though the research that is available suggests that such effects are likely. This paper reviews the available evidence regarding the relationships between community context and methadone treatment program outcomes, and suggests directions for future program and research efforts in this relatively ignored area.

WHAT IS COMMUNITY?

The community context of methadone treatment can be viewed in at least five ways. Each represents a potentially useful perspective for understanding the ecological context of drug abuse treatment. The five views of community are:

1. A geographical environment defined by the sociodemographic characteristics of residents.

2. A set of organizations which an individual may encounter.

3. A culture, a set of expectations and beliefs localized in a geographical setting.

4. A neighborhood in which people carry out their daily routine and with which they may identify.

5. The people with whom an individual interacts in the routines of daily living.

Each of these views of community has possible implications for drug abuse treatment though these implications

rarely have been studied. The research on each community context and methadone maintenance is reviewed below.

Community: A Geographical Environment Defined by the Socioeconomic Characteristics of Residents

This is perhaps the most objective and hence most easily researched of the five views of community. Research on community defined in this way involves fixing the geographical boundaries of a community, selecting a set of sociodemographic variables associated with the chosen area, and then comparing outcomes across programs in different communities. Only one study of methadone maintenance programs has investigated the relationship between community and client outcomes in this way. Joe et al. (1977) analyzed the Drug Abuse Reporting Program (DARP) 1971-1973 admission data to determine how youth, sex ratios, race, unemployment, and property crime rates in census tracts around methadone programs were related to client functioning during treatment. Client opioid use, nonopioid use, employment, productive activities, and criminal activities were assessed. Combined, the community variables, taken from the 1970 census data, explained a maximum of 9.1 percent of the variance in nonopioid use and a minimum of 2.2 percent of the variance in criminal activity of 1,336 clients admitted to 15 methadone maintenance programs. Individually, the ethnicity and male unemployment community characteristics were moderately correlated with, at most, two of the client outcome criteria, though no strong consistent pattern of zero order correlations emerged. The most consistent finding was that the proportion of Puerto Ricans in a community was moderately related to poorer client functioning in employment ($r = .25$) and productive activities ($r = .27$). The proportion of Hispanics in a community was related to more opiate use during treatment ($r = .21$), and the proportion of Hispanic families in poverty was related to poorer employment during treatment ($r = .18$). These correlations are stronger than the zero order relations between individual client ethnicity and outcomes.

Thus, community ethnicity appears to be a contextual variable which is related to treatment outcome. The data suggest that contextual variables in combination with other client characteristics may be more important than

an individual client's race per se in determining treatment outcome (Joe et al. 1977). These findings have important implications. They suggest that research on treatment effectiveness should attend to the possible effects of community characteristics if client outcomes are to be understood. Apparently, client outcomes cannot be attributed simply to the effects of methadone or to individual client characteristics. Clients in methadone maintenance programs in certain ethnic minority communities may have lower probabilities of outcome success. Unfortunately, the available data do not indicate whether these poorer outcomes result from decreased opportunities for employment and productive activities in these communities, to particular norms of these communities, or to some combination of factors.

Community: A Set of Organizations Which an Individual May Encounter

This second perspective views communities as opportunity structures encountered by clients. Opportunities are determined both by structural and economic conditions and by the practices of organizations and agencies in a particular area. For example, institutional barriers to the employment of former drug abusers have been widely recognized. Despite provisions of Federal law (PL 92-225) preventing discrimination in employment by reason of previous drug abuse, there is evidence of widespread resistance by both public and private employers to the employment of present and former methadone clients. Only 28 percent of a sample of New Jersey employers anonymously surveyed by Pugliese (1974) reported that they would hire a methadone client. The New York Transit Authority had, prior to the Beazer vs New York City Transit Authority case, a policy of excluding all former heroin addicts participating in methadone maintenance programs from any form of employment in the New York City subway and bus systems (Legal Action Center 1977). Discriminatory practices of employers, social service delivery organizations, and educational institutions represent community characteristics which may decrease the chances that methadone clients are able to secure employment, education, and the services needed to function successfully in the community. While methadone program evaluations have shown that many clients are employable (Gearing 1974), and while supported work programs (Manpower Demonstration Research Corporation 1980) and legal advocacy efforts (Legal Action Center 1977) appear to be

effective means of increasing the successful employment of former drug abusers, I am aware of no studies which have attempted to link directly the practices of a set of surrounding community organizations and the outcomes experienced by methadone clients during or after treatment. There is little information about the extent to which the client outcomes reported in treatment program evaluations are related to the practices of surrounding community organizations.

However, Pittel's (1978) research reveals widespread institutional practices which could inhibit the successful community adjustment of treated drug abusers. Pittel and his staff interviewed representatives of a broad range of the public and private social service agencies in Alameda County, California, regarding policies, practices, and attitudes toward former drug abusers. While the results of the study were not linked to client outcomes, they reveal agency practices and biases against drug program clients which seem likely to inhibit successful community integration and rehabilitation.

Pittel found a bias against addicts in vocational training and placement agencies:

> Since (vocational training and placement) program futures are often dependent on the number of job placements, several agencies look skeptically at applicants who have histories of either drug abuse or criminal involvement. These agencies minimize their risk by not selecting applicants with multiple problems and poor work histories... A representative of one vocational training agency would not grant an interview because the agency does not serve former heroin addicts "when there are plenty of good citizens, recent high school graduates, and others who never got into any trouble and who are out of work." (Pittel 1978)

Pittel found a general pattern of attitudes and practices unfavorable to former drug abusers. Five of ten housing agencies reported problems in serving addicts and ex-addicts. Two agencies anticipated problems related to landlords not wanting to rent to former addicts, and four expected that the behavioral problems of former addicts would interfere with service delivery efforts. All the family counseling programs surveyed anticipated problems serving former addicts because of individual psychopathology, community attitudes, and inadequate training for

dealing with such clients. Child care agencies also expected problems in serving former heroin addicts and their families. The alcoholism treatment programs in the county would not accept clients with a combined drug and alcohol abuse history. Thirteen of the 15 mental health aftercare services surveyed anticipated problems in serving former addicts, citing relapse to an addict lifestyle and lack of community support as reasons for the anticipated difficulties. Most of the mental health aftercare agencies surveyed would not serve methadone clients because they defined drug abuse as the major problem of such individuals. They referred people with drug abuse problems to substance abuse clinics.

Pittel's findings suggest that methadone clients may have difficulties in securing from community organizations the basic services needed to find housing, a job, assistance with children, and assistance with individual adjustment. Yet these are the kinds of practical assistance that former addicts are likely to need to become effective functioning members of the community.

Barriers to obtaining these services from community agencies are particularly salient when the evidence regarding service availability in methadone programs themselves is considered. In the Alameda County study, Pittel found that of 10 methadone maintenance programs, only three provided vocational services; none provided education classes (such as GED preparation programs); none provided financial counseling services; none provided dental services or money for dental services; none provided housing services or referrals; none taught basic household skills (such as meal preparation, grocery shopping on a budget, or planning menus); none provided direct services for the treatment of ancillary alcoholism; three provided family therapy services; and one provided aftercare support group meetings for graduates. While this apparent paucity of services beyond the distribution of methadone may not characterize all methadone maintenance programs, there is evidence that methadone programs generally are not staffed to provide a wide range of services. Research has shown that there are "strikingly fewer full-time therapy/counseling staff available to methadone maintenance clients than is true of other modalities" (NIDA 1979). The overall staff to client ratio in methadone maintenance programs is 1 to 25 as compared with 1 to 17 in drug free outpatient programs and 1 to 5 in residential treatment programs. For counselors with degrees, the comparative staff to client ratios are 1 to

289 (methadone maintenance), 1 to 99 (drug free outpatient), and 1 to 52 (residential treatment); for therapy staff without degrees they are 1 to 116, 1 to 63, and 1 to 9 across the three modalities, and for vocational specialists they are 1 to 2,139, 1 to 700, and 1 to 109 across the three modalities (NIDA 1979).

These data suggest a dilemma. Methadone maintenance programs do not appear likely to provide the ancillary services which can help clients function more effectively in the community, especially following treatment. Yet there appear to be policy, procedural, and attitudinal barriers which inhibit former drug abusers from using the services of other organizations in the community. Community service organizations generally anticipate problems in dealing with former drug abusers, and, in many instances, prefer not to serve these people, referring them back to a drug treatment program if possible. Even where services are available without prejudice, the complicated procedures and eligibility requirements of many agencies may discourage use by former heroin addicts (Pittel 1978).

In summary, while the direct effects of the policies, practices, and attitudes of community organizations on the outcomes of methadone maintenance clients have not been studied, it appears reasonable to suspect that they present limited opportunity structures which decrease the chances of successful integration of the former abuser into the larger society.

Community: A Culture, a Set of Expectations and Beliefs Localized in a Geographical Setting

Pittel's finding regarding service providers' expectations of former heroin abusers suggests another set of community variables which potentially affect treatment outcomes. The attitudes of community members provide a normative context in which methadone treatment takes place. That context of beliefs and expectations regarding methadone clients may have both direct and indirect consequences for treatment outcomes. Community beliefs and expectations may affect clients' own attitudes toward themselves (Brown et al. 1975b). These attitudes are likely to affect treatment outcomes, as has been documented in the mental health field (Goldstein 1962; Lennard and Bernstein 1960; Sloan et al. 1970).

Despite the relatively positive results of methadone maintenance evaluations summarized in other chapters of this volume, methadone maintenance continues to be a highly politicized treatment approach. The use of a synthetic opiate to treat opiate dependence is, in part, a response to the social stigma and illegal status of heroin. A direct consequence is that methadone maintenance programs are subject to criticism as drug substitution rather than drug treatment.

Research on community, treatment staff, and client beliefs has consistently revealed an ambivalence about methadone maintenance. While a survey (Bower 1978) in Washington, DC, showed that community members generally viewed methadone as permitting drug-dependent individuals to adopt normal lifestyles, respondents also viewed the use of methadone as simply replacing one addiction with another (Brown et al. 1975a). These community views appear to be reflected in the attitudes of drug treatment staffs and clients.

Brown et al. (1975a) and Sutker et al. (1978) conducted opinion surveys of drug treatment clients in different treatment modalities in two major metropolitan areas. Additionally, Brown et al. (1975b) compared staff and client attitudes toward drug treatment programs and their clients. Several results from these studies are notable. First, methadone clients generally agreed that methadone is a helpful tool in taking away the craving for heroin. Seventy-eight percent of the 190 methadone client respondents in Brown et al.'s study (1975a) agreed with this proposition. Similarly, 80 percent of the surveyed clients agreed that methadone can help people free themselves from the use of drugs over time (Brown et al. 1975a). However, these clients also tended to see methadone as a tool of social control and minority repression. Seventy-one percent of Brown's methadone client respondents agreed that methadone has been used more to stop crime than to help addicts, and 64.7 percent agreed that methadone represents an oppression of a black minority by a white majority (Brown et al. 1975a). A large minority of methadone clients feared methadone itself. Nearly 47 percent feared that "methadone will become a bigger problem than heroin ever was." Eighty-three percent agreed that "it's harder to get off methadone than it is to get off heroin." Eighty-eight percent agreed that taking methadone is only replacing one addiction with another, and over 68 percent viewed methadone as a crutch. Forty-six percent of the surveyed clients in methadone

programs disagreed with the statement that methadone has proven to be the best way to quit heroin use (Brown et al. 1975a). According to Brown et al. (1975a), "In the client's view methadone's usefulness as a treatment technique is undeniable, but it remains a suspect drug."

Given these ambivalent views toward methadone among both community members and methadone clients, it is not surprising to learn that methadone clients are generally viewed by both treatment staff and clients as inferior to clients of other modalities (Brown et al. 1975b; Sutker et al. 1978). This view is shared universally by clients and staff of therapeutic communities, outpatient drug free programs, and methadone programs. In Sutker et al.'s (1978) research in New Orleans using the Adjective Check List (Gough and Heilburn 1965), methadone clients were viewed consistently as more aggressive, less well adjusted, and less self-confident than clients in other treatment modalities. In Brown et al.'s (1975b) studies of Washington, DC, treatment staffs and clients, views of heroin users and drug abstinent clients did not change from 1970 to 1973. However, both groups' views on methadone maintenance clients changed substantially and in negative directions. Methadone clients were increasingly viewed as lower on measures of prosocial striving and forcefulness in social relations and higher on measures of introspection, concern with social approval, and passivity in dealing with the world. Moreover, drug program staffs and clients consistently viewed both methadone maintenance clients and heroin addicts as less effective in the community than abstinent clients (Brown et al. 1975b).

These consistent findings regarding attitudes toward methadone maintenance and methadone clients suggest the existence of a widespread set of beliefs which may have important implications for methadone maintenance programs, as well as for client outcomes. Brown et al. (1975a) state:

> It seems safe to say that methadone can never gain acceptance on the basis of scientifically demonstrated merit alone. To gain acceptance with the consumer (addict) community, methadone must overcome or circumvent the hostility and suspiciousness that often characterize white/nonwhite relations.

To the extent that methadone maintenance programs are viewed simultaneously by community and clients "as mechanisms to sustain dependence on a drug identified with

sedative effects and to minimize encounters with law enforcement" (Sutker et al. 1978), ambivalence toward this treatment modality will likely remain widespread and support for methadone maintenance programs will be equivocal. The politicization of methadone maintenance may require methadone programs to adopt community positions and program services which enhance their community support, especially in an era of social program cutbacks, competition for scarce treatment resources, and a decreasing consensus regarding the existence of a heroin epidemic. From a perspective of program maintenance, it may be important to initiate service components which clearly facilitate development of productive activities, personal independence, and achievement orientation among clients.

This suggestion appears reasonable from a rehabilitation perspective as well. If methadone clients view themselves as the most disabled of drug clients in terms of exaggerated dependency needs and excessive demands for interpersonal support and attention (Sutker et al. 1978), it may be important to structure services in methadone programs to address explicitly these perceived interpersonal problems.

The commonly shared beliefs about methadone and methadone clients also appear to have important implications for client retention in treatment and hence for client outcomes. Brown et al. (1975a) have suggested that clients' concerns about methadone are likely to develop after they are in treatment and have begun to feel some control over heroin use. At this point, in the face of negative community attitudes and self-perceptions, clients may seek a route out of a stigmatized dependent status and leave treatment early to salvage self-respect (Brown et al. 1975b). In light of the growing consensus that "successful stabilization on methadone maintenance is a necessary prerequisite to detoxification and drug-free living" (McClellan, this volume, part III, chapter 1), the risk of early termination from methadone treatment appears particularly worrisome. Community, staff, and client beliefs about methadone may influence against treatment retention in methadone maintenance. These beliefs may, therefore, negatively influence client outcomes. While there is reason to suspect that widely shared beliefs about methadone maintenance may have a negative influence on client outcomes, no direct evidence is available regarding the existence or the strength of such a relationship.

Community: A Neighborhood in Which People Carry Out Their Daily Routines and with Which They May Identify

Local neighborhoods were viewed by sociologists of the Chicago school as the building blocks of urban social organization, the important foci of personal, social, and political life within cities (Burgess 1925; Hunter 1974; Park 1952; Suttles 1972). Subsequent sociological work viewed the local community area as an important, though limited, mechanism for shielding the individual from the impersonality of urban life (Greer 1962). More recent studies have focused on the extent and nature of attachment to neighborhoods and local areas (Guest 1978). Common to all these perspectives is the assumption that small geographical subunits of urban areas may elicit the cognitive, affective, and behavioral attention and attachment of residents (Guest 1978). They are places with which people may identify and in whose behalf people may invest time and energy.

There are several ways in which neighborhoods, so conceived, might affect methadone programs and outcomes. Most obvious is the possible mobilization of residents in support or opposition to the existence of a methadone program in a neighborhood. In the era of expansion of methadone maintenance programs, this was an issue which generated concern as well as strategies for minimizing neighborhood opposition (cf. Lowinson and Langrod 1975; Ruiz et al. 1975). To the extent that effective treatment requires reintegration of methadone clients into local neighborhoods, local area support or opposition would appear to remain an important issue, although it has not continued to receive much published research attention. I am aware of no recent research seeking to link such neighborhood variables with methadone client outcomes.

If they are relatively homogeneous and well integrated systems of shared values, neighborhoods may also influence drug treatment outcomes in another way. If neighborhood residents value the roles associated with street drug use, such as hustling, pimping, and dealing, neighborhoods may act as subcultures which influence residents to maintain deviant patterns of living regardless of the efforts of drug treatment programs. This perspective is consistent with cultural deviance theory, which suggests that deviance occurs because behavioral norms within subgroups of society have such variations that the standards of some subcultures are inherently deviant when compared with those of the dominant social group (Sutherland 1956). In

contrast, if neighborhood residents generally oppose drug use, neighborhoods may act as agents of informal social control which influence their residents toward more conventional patterns of living.

The studies in the drug field most relevant to this neighborhood perspective are the ethnographic investigations of heroin copping areas in Chicago conducted by Hughes and his associates (Hughes and Jaffe 1971; Hughes et al. 1971, 1974). Their research revealed that copping area neighborhoods were loosely coupled rather than tightly integrated residential subcultures. A majority of the sample of interviewed neighborhood residents simply were not aware of the existence of a heroin copping area on their block (Hughes et al. 1974). Moreover, even where addicts were ostensibly linked to their neighborhoods as suppliers of stolen goods, a minority of neighborhood residents were involved (Hughes et al. 1974). In summary, Hughes and his associates found that neighborhood residents had little knowledge or contact with the addicts who frequented their corner copping areas. To the extent that a deviant subculture of drug abusers exists in a neighborhood area, it is not synonymous with the neighborhood itself. It appears from Hughes' work that neighborhoods are not integrated sufficiently to serve as consistent influences for or against drug abuse. If such influences exist, they are more likely to be found in the circle of friends with whom people routinely interact. This suggestion leads to a final perspective on communities and drug abuse treatment.

Community: The People with Whom an Individual Interacts in the Routines of Daily Living

This final view of community focuses on the system of interaction in which an individual is embedded, or more simply put, the people whom one sees and with whom one talks each day. In essence, this is the most immediate social or ecological context which may affect the individual. It is the subject of the growing field of social network analysis.

As defined by Mitchell (1969), a social network is a "...specific set of linkages among a defined set of persons, with the additional property that the characteristics of these linkages as a whole may be used to interpret the social behavior of the persons involved." Social networks can be viewed as the connections between people through which beliefs and attitudes are shared, through

which the policies and practices of organizations are experienced, and through which the events of local neighborhoods are transmitted. As such, they are a kind of lowest common denominator of community, though they are distinct from communities as described previously in that they are not defined by common geographical boundaries. A person's social network may include members who live and act in a number of very different locales.

The social network perspective on behavior is useful because social networks include those members of an individual's social environment who are likely to have the most immediate and direct impact on behavior. These are the people with whom the individual interacts. In contrast to neighborhood residents whom the individual may not even know (Hughes et al. 1974), network members are likely to support and reinforce patterns of behavior, whether conventional (Phillips 1981) or deviant (Cohen 1955).

Unfortunately, there are few studies of social networks in the drug field and no published studies of the relationships between social networks and drug abuse treatment outcomes. Killworth and Bernard (1974) applied network analysis to offenders, but their study was limited to a small prison living unit. Pattison et al. (1979) studied addict, alcoholic, normal, and a variety of psychiatric populations, but reported no sampling procedures and little empirical evidence to support their conclusions.

Research completed by my colleagues and myself (Hawkins and Fraser 1981) has sought to extend understanding of the relationships between communities and drug abuse by users' social networks before and after treatment. Our research was conducted with a sample of 106 subjects from four therapeutic communities in two metropolitan areas of the western United States. We followed 49 of these subjects to conduct 1-month and 3-month interviews following treatment. Subjects in the study ranged in age from 16 to 18 ($\bar{x}$ = 28 years). Seventy-six percent were Hispanic and 20 percent were black. Seventy percent had used heroin. Seventy-five percent had committed illegal acts beyond drug possession in the 30 days prior to treatment.

We found that users' pretreatment social networks contained substantial proportions of both drug users (42.5 percent) and people who used only alcohol or no psychoactive drugs (32.4 percent). Yet those who used opiates several times a week or more in the month prior to treatment appeared to have much more deviant social networks

than did users of other drugs. Opiate users' networks provided stronger support for drug use and contained significantly fewer members who used only marijuana or alcohol than did the networks of those who used other drugs. Further, pretreatment opiate use was also related to the proportion of social network members from socially acceptable areas of involvement. Opiate users had significantly fewer contacts from work, school, and organizations, and significantly more street crime and drug business contacts than did users of other drugs at entry to treatment. Opiate users' networks were characterized by a particularly deviant membership, with fewer members from conventional settings beyond the family. The data suggest that opiate users entering treatment have social relationships in which drug use and criminal behavior are valued positively by peers who have virtually no stake in more socially acceptable activities.

Our study also revealed a positive relationship between opiate use following residential treatment and the proportion of posttreatment network members who used drugs. Over 20 percent of the posttreatment network members of those who used opiates in the first month following treatment were themselves frequent users of drugs. In contrast, those who did not use opiates in the first month following treatment had an average of only 3.4 percent regular users in their networks. While the social networks of all subjects changed in membership from before treatment to 1-month follow-up, those who used opiates in the first 3 months following treatment had posttreatment networks which provided greater support for drug use than did those who did not use opiates in this period.

The findings of our research indicate that social networks are communities of individuals which are related to patterns of drug use and to treatment outcomes. Social network support appears to be a factor in drug use both before and after treatment. It would appear that methadone clinics should seek to assess and address this community characteristic of their patients. Our research suggests that a goal for methadone programs should be to help patients to alter the composition of their social networks in order to eliminate the members who are supportive of drug use. Our research indicates that former drug abusers need to become connected with people involved in more conventional rounds of activities if they are to drop ties to drug abusing peers (see also Waldorf and Biernacki 1981).

The data from our study suggest that the key to ensuring this is to assist clients to connect with new people whom they admire and respect, people whom they can view as role models (see also Waldorf 1973). Only this variable of esteem for network members appears to be consistently lacking in the pretreatment relationships of drug abusers and their networks. It is precisely this element of wanting to be like network members which appears to be absent when networks are predominated by drug users and drug business associates.

Our results suggest that three conditions should be met if the social factors contributing to drug abuse are to be adequately addressed in methadone clinics:

1. Support in the social network for drug abuse should be minimized or eliminated.

2. Clients should be linked to new network members who are engaged in conventional activities, and who can provide the attachment and support formerly provided by a network more strongly supportive of drug use (Stanton 1979; Waldorf and Biernacki 1981; Wolf and Kerr 1979).

3. Special care should be taken to ensure that the new network contains viable role models whom the former abuser holds in high esteem.

These criteria simultaneously imply broadened roles for methadone clinic staffs in the rehabilitation process while suggesting very real limits to what can be achieved through formal treatment services. Traditional services are not likely to directly affect the primary relationships between clients and their social networks, nor are they likely to provide, on a daily basis, the attachment and support necessary for the replacement of network members supportive of drug abuse (Hawkins 1979). For these reasons, methadone staffs may need to use broadened models of service to supplement traditional approaches. This will require a basic shift in orientation for many treatment staffs away from the accustomed technology of counseling (Brown 1979).

To accomplish a transformation in community networks, treatment staffs may need to become consultants and facilitators to social network members and community volunteers, who will themselves become the bonding nuclei of new networks. In this process, the role of staff will

shift away from direct services for clients and toward recruitment, orientation, training, and consultation to community volunteers and natural network members (see Hawkins 1979).

CONCLUSION

We had investigated five views of community as a possible contributor to methadone maintenance program outcomes, finding little research on methadone maintenance founded in any of these views. However, almost all of the research which is available suggests the possible importance of the community context in influencing client outcomes. In the few cases in which the relationship between community context and client outcome has been assessed, there is evidence that community variables do, in fact, influence outcomes (cf. Joe et al. 1977; Hawkins and Fraser 1981).

This evidence indicates that it will be productive to pursue a program of research on the relationship between the ecology of drug abuse treatment and client outcomes. With the possible exception of neighborhood studies, all of the approaches to community research considered here appear to hold promise for a better understanding of methadone client outcomes. Generally, it appears that community factors are likely to have a negative effect on outcomes unless adequately addressed by treatment policies and programs. To achieve the goal of more effective treatment, it will be important to understand the relationships between community characteristics and treatment outcomes so that community factors which inhibit treatment success can be addressed by drug policies and programs.

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CRITIQUE

Richard J. Russo, M.S.P.H.

The author of this paper, J. David Hawkins, has done an excellent job in reviewing and presenting the current state of the art regarding community characteristics as they relate to treatment and outcome for methadone maintenance patients. Unfortunately, the research in this area has been sparse, and there is very little documentation in the professional literature to substantiate and/or refute the hypothesis that "community characteristics provide a negative or a positive influence on the return of a methadone maintenance patient into a community setting."

In an effort to keep this reaction short, I will address my comments to specific items, issues, and/or statements in the original paper.

The author states that "drug abuse treatment programs do not seek merely to stop the illicit use of drugs, but rather to assist people who no longer are functioning effectively in legitimate society, whether personally, socially, or emotionally, to adopt different patterns of lifestyle." I do not believe there is consensus in the substance abuse field to this statement. In fact, I am quite certain that a portion of the methadone maintenance drug treatment programs do "seek merely to stop the illicit use of drugs." If one researches the early literature on methadone maintenance and the heroin epidemic of the late 1960s, one can conclude that methadone maintenance programing was specifically designed to stop or interrupt the illicit use of heroin with an ultimate, primary goal to reduce the amount of crime in our cities. I believe the goal of drug abuse treatment programs "to assist people who are functioning ineffectively in society to adopt different, more positive patterns of living" was secondary, and perhaps an afterthought, following the major emphasis to reduce crime in our streets.

The author also states, "If treatment is to be effective in realizing the broader goal of social rehabilitation, it must address the social factors related to the initiation, maintenance, and return to drug abuse." It is interesting to note that if future research substantiates

the theory that opiate addiction is related to a biochemical imbalance and this imbalance is a causal factor for drug use, then the need for "social factors" intervention may be reduced or even eliminated.

This paper reviews the current available knowledge regarding the relationship between community context and methadone treatment program outcomes and, unfortunately, there is very little information available on this topic. However, I believe most, if not all, methadone maintenance programs in this country do not relocate their clients from the community which spawned their addiction in the first place. This makes the relationships between the client and the community very difficult to evaluate because in most instances the relationships do not change before, during, and after the time that a client is on a maintenance program.

The main portion of the paper under review identifies five "views" of the community which are presented to provide a useful perspective for understanding the ecological context of drug abuse treatment. The five views of the community as expressed in the paper are:

(1) a geographical environment defined by the sociodemographic characteristics of residents;

(2) a set of organizations which an individual may encounter;

(3) a culture, a set of expectations and beliefs localized in a geographical setting;

(4) a neighborhood in which people carry out their daily routines and with which they may identify; and

(5) the people with whom an individual interacts in the routines of daily living.

It appears to me that each of these above-mentioned five views has possible implications for methadone maintenance client outcomes. However, I perceive a sixth "view" as follows: Where does the everpresent, everchanging "community politic" fit into this process? The "community politic" I refer to can be expressed in the form of a local ordinance that may forbid the establishment of a methadone maintenance program; or in the emphasis that is

placed on law enforcement efforts which can change in intensity from week to week. These "community politic" decisions can have a dramatic effect on the reintegration of a methadone maintenance patient back into a community setting. The fact that methadone maintenance programs are outlawed by ordinance in a community, or that law enforcement makes a concentrated effort to arrest all active drug abusers, may have a very negative effect on the client who is attempting to reintegrate into the very community which is ostracizing all substance abusers.

In the discussion of the first view of the community, "a geographical environment defined by the socioeconomic characteristics of the residents," the author indicates that clients in methadone maintenance programs in certain ethnic minority communities may have lower potential of successful outcome. He further indicates that these poorer outcomes result from decreased opportunities for employment and productive activities in these communities. I believe there is more involved in decreased employment of ethnic minorities than fewer job opportunities. I believe we generally err in not attempting to match our clients with the kinds of employment for which they are most suited, and these jobs should be acceptable to communities. We often attempt to push our recovering substance abusers into sensitive jobs which further enhance the potential for failure. As an example, I don't believe it is wise for us to attempt to take a recovering alcoholic and turn him or her into a bartender; nor is it desirable to place a recovering drug abuser in employment on a production or packaging line of an ethical pharmaceutical manufacturer where controlled dangerous substances exist. Furthermore, we should not attempt to place a methadone maintenance client behind the controls of a high speed train, or a bus. Even though we as professionals in the substance abuse field know that a well maintained methadone client can function normally in a sensitive community position, the community at large does not share our trust in the client. Therefore, to alleviate undue pressure on our clients, we should not attempt to place methadone maintenance clients in sensitive positions until the community is ready to accept and trust them.

I stated earlier that we should attempt to match a client with appropriate employment acceptable to the community, and I would like to refer to a small employment project conducted in New Jersey which demonstrates this match. We involved the casino industry in the Atlantic City

"boom" community and developed an employment training program that would fit the needs of the casino industry. The specific need identified was for entry level food service handlers, and based on this realization, an 8-week culinary arts training program was designed and implemented. Food service staff of several casinos were actively involved in the actual training for this culinary arts program, which culminated in the graduation of nine recovering substance abusers who all found full-time employment in the casino food service area. At the time of this writing, which is approximately 6 months after graduation from the culinary arts training program, all nine recovered substance abusers have retained their employment, and the employers are extremely pleased with the clients we sent them.

Reference was made in the paper to Dr. Steve Pittel's 1978 research in Alameda County, California in which Dr. Pittel found a bias against addicts in the existing vocational training and placement agencies. Dr. Pittel found that most of these existing agencies made a conscious effort not to select recovering drug clients because of their multiple problems and poor work histories. Dr. Pittel's finding is not unique, and I suggest that perhaps the best way to circumvent the existing vocational training and placement agency is to develop our own specialized independent capability in this area. This approach is only economically feasible in a rather large geographic area where there are a significant number of recovering drug abuse clients who can be filtered through the independent vocational training and placement agency. In New Jersey, this specialized vocational training and placement effort has been working very well.

Under the third view of the community as "a culture, a set of expectations and beliefs localized in a geographical setting," the author specifies that "in the client's view methadone's usefulness as a treatment technique is undeniable, but it remains a suspect drug." Unfortunately, this perception of methadone is not only shared by the client but is very evident in the minds of legislators, politicians, and, yes, even in the minds of some well trained public health professionals.

In the fourth view of the community, "a neighborhood in which people carry out their daily routines and with which they may identify," the author states, "if neighborhood residents generally oppose drug use, neighborhoods may act as agents of informal social control which

influence their residents toward more conventional patterns of living." In my involvement in the substance abuse field, I have not found this to be true. In fact, most neighborhoods with which I am familiar that generally oppose drug abuse, do not influence their residents toward more conventional patterns of living; in fact, they appear to exacerbate the drug abuse lifestyle of their residents.

The fifth and final "view" of community "is the people with whom an individual interacts in the routines of daily living." This last part of the paper is a summary of a study carried out by Hawkins and his colleagues. The subjects in the study were residents in four residential drug treatment centers (therapeutic communities), two treatment programs in a northwest city, and two in a western city which were selected to guard against local geographic effects. The focus of the research effort was the community reintegration of treated clients from these residential treatment programs.

REACTION 1

I realize the constraints of conducting a study which would be truly representative of cities throughout our country. However, I believe the fact that this study was conducted exclusively on the west coast lends a bias to the results. The reintegration problems of opiate users back into western cities may be significantly different than the reintegration problems in some of the northeastern high impact cities such as New York, Newark, New Jersey, Washington, DC, etc.

REACTION 2

The number of subjects interviewed may be too small to draw valid conclusions. Although I found the results of the study most interesting, they reinforced my perceptions regarding drug abuse treatment: with our present state of knowledge there is no consensus about how social factors interact in the ecology of drug use and abuse. As expressed by the Drug Abuse Council in their final document, "The underlying social dynamics and problems that lead to drug misuse are so exceedingly complex as to as yet elude totally satisfactory solutions"; we still have a very long way to go.

One interesting result of this study was that many respondents indicated that they did not want to be like those social network members who are engaged in illicit street traffic in goods and drugs, nor did they want to emulate hard drug users. While these findings are only suggestive, they have important implications for rehabilitation. Attachment in social networks is a complex issue which, as Hawkins points out, includes elements of affection, identification, imitation, reciprocity, and duration. Aspects of this bond may develop regardless of whether network members are engaged in deviant behavior. Fortunately from a rehabilitation perspective, the imitation or role modeling element of attachment appears negatively related to the deviance of network members. Another important finding from this study is that returning clients appear to establish more conventional networks of interaction during their first months back in the community following residential treatment, and there is some evidence that relapse is more likely if returning clients do not establish networks which provide consistent effective support and which do not include role models deemed worthy of emulation.

REACTION 3

I completely agree that relapse is more likely if returning clients do not establish networks which provide consistent, effective support. However, how does one explain the extremely high relapse rate among some clients who do establish significant consistent support networks which also include positive role models?

This study seems to confirm several propositions with regard to opiate abusers' pretreatment social networks. The study reports that clients in the 3 months prior to treatment reported significantly more people in their networks who influence them to use drugs than were in their networks for the first 3 months posttreatment. Statements in this paper indicate that an important goal for community based treatment programs which serve opiate abusers should be to help clients to alter the composition of their social networks in order to eliminate the members who are supportive of drug use. The paper further states that clients who remain in residential treatment for at least 3 months appear to establish posttreatment networks which are less oriented toward drug use and less supportive of a return to drugs. Nonresidential

programs such as methadone maintenance clinics cannot expect that their clients' network ties supportive of drug use will be broken simply by virtue of treatment participation. As long as methadone and other outpatient clients continue to reside and participate in neighborhoods where they have routine contact with their network members, it will take an intentional effort to cut the ties that influence them to use illegal opiates. The study further states that treatment program participation may provide some of the conditions necessary to break these old ties, but such participation is unlikely to be sufficient to cause the ties to be severed unless this becomes an explicit treatment goal.

REACTION 4

That treatment program staff participation is necessary to break old network ties, and that developing new, more positive networks for clients should become an explicit treatment goal may be a desirable program effort. However, in light of the major fiscal reductions facing drug treatment throughout the country, this task probably will be impossible for treatment staff to accomplish without major reductions in other supportive treatment efforts.

Hawkins' paper identifies three specific conditions which should be met if the social factors contributing to drug abuse are to be addressed in methadone maintenance, therapeutic communities, or other treatment programs which serve opiate abusers. These conditions are as follows: (1) support in the old social network for drug abuse should be minimized or eliminated; (2) clients should be linked to new network members who are engaged in conventional activities and who can provide the attachment and support formerly provided by a network more strongly supportive of drug use; and (3) special care should be taken to ensure that the new network contains viable role models whom the former abuser holds in high esteem. These three conditions imply a much broadened role for drug treatment programs staffs in the rehabilitation process, while suggesting very real limits to what treatment personnel can expect to achieve through formal treatment services.

It is important to recognize that traditional counseling or other client focused services to people living in their natural social environments are not likely to affect directly the primary relationships between clients

and the social networks, nor are they very likely to provide on a daily basis the range of attachment and effective support necessary for the replacement of a network supportive of drug abuse. For those reasons, the paper emphasizes that treatment staffs will need to use broadened models of service delivery to supplement traditional treatment and counseling approaches, and this will require a basic shift in orientation for many treatment staffs away from the accustomed technology of the medical profession in which the client comes to the treater for resolution of problems in the treatment setting.

To accomplish a transformation in community networks, the paper suggests that treatment staffs will have to become "consultants, facilitators to social network members and community volunteers who will themselves become the bonding nuclei of new networks. In this process, the role of staff will shift away from direct service for clients toward recruitment, orientation, training, and consultation to community leaders, volunteers, and natural network members." It is suggested that we in drug abuse treatment should model our re-networking of clients back into communities similarly to the community reintegration of former mental patients, sometimes referred to as deinstitutionalization.

The author states that achieving the reintegration criteria implies an expanded role for the larger community, in that the school, work, and other organizational settings should become involved to produce supportive links with members of these groups, and these members will have to become actively involved with former drug abusers in the reintegration process back into communities. There is strong evidence from the mental health field of the importance of community acceptance and support of former patients in determining positive client outcomes.

The paper concludes with an explanation of several general approaches to social support development which may hold promise for former drug abusers in networks supportive of rehabilitated lives. These general approaches take the form of consultation to existing network members, collaborative consultation, network assemblies, formation of new social supports and activities model, a skills training and recreation companionship model, a home placements model, a community employment model, and a community lodges model.

Hawkins believes all of these approaches or models mentioned above stress the active involvement of community members in creating supportive networks for exabusers, and that active community participation is generally missing from rehabilitation programs. Professional treatment staff should not simply design and implement programs oriented towards supportive network development which include opportunities for community volunteers; rather, the very process of program development should be one of collaborative consultation among treatment professionals and members of community groups. Community groups should participate from the start in developing and appraising models, and realistically assessing the abilities of their members to implement them.

REACTION 5

My reaction to the statements enumerated above, which were paraphrased from the paper, is one of bewilderment. At a time when major fiscal support for the provision of drug abuse treatment services is dwindling, how can one expand treatment activities to include major community networking for clients as identified in this paper?

Perhaps the most logical way to approach the networking issues would be to attempt to demonstrate the feasibility of this approach by pilot testing one or two programs in a circumscribed geographic area to ascertain whether or not the shift in program emphasis and treatment goals will produce any greater desired positive results in the rehabilitation process and reintegration back into communities. Without a demonstration model and longitudinal evaluation, I would be hesitant to follow the approach as suggested by this study.

Adequate evidence has not been presented to demonstrate that major networking will produce a greater number of long-term rehabilitated clients. It appears to me that empirically we should support the establishment of treatment program involvement in developing positive networks for the substance abuser prior to his reintegration into the community. However, I doubt if it is possible for drug treatment programs in this country to actively engage in this process at this time because of the time-consuming aspects and additional staff involvement that this would entail. Perhaps the best we can do in the real world (when that world is significantly shrinking in support) is to concentrate our efforts in one proven

area, "skills training." Developing linkages with community members to provide skills training and job placement support appears to be one the most effective tools for reintegration of clients back into communities. Focusing on employment seems to be central in defining roles and identities in our society, and employment has one of the greatest potentials for providing positive community networking. The National Supported Work Demonstration Project demonstrated the effectiveness of employment as a major reintegration process.

In New Jersey, we recently concluded a survey of over 1,000 methadone maintenance clients, at which time we attempted to determine the clients' employment and employability status along with their "perceived need" for vocational services. This survey clearly showed that within the relatively stable methadone maintenance client population, approximately 40 percent were underemployed, and the vast majority were inadequately prepared for successful integration into society because of low academic and vocational skills achievement. One of the most important results from this survey was that the clients themselves recognized these deficiencies, and they expressed a desire for more viable vocational related programing to improve their potential for reintegration back into their communities. The clients were asking for tangible, practical services which could assist them in feeling more positive about themselves and their social status. They wanted services that could help them develop a more positive self image, better health, and employment, and educational services to assist in their community "reintegration" process.

In conclusion, perhaps we in substance abuse should take a lesson from the mental health field and their utilization of the "Linkage Mental Health Worker." The Linkage Mental Health Worker focuses on facilitating the delivery of traditional mental health services to primary care consumers by improving the channels of referral and often by providing onsite mental health services. A drug abuse Linkage Worker could provide new and exciting emphasis toward the objective of saving and prolonging community life through the development of a positive networking system aimed toward the modification of behavior.

The Linkage Mental Health Worker model includes a major emphasis on the behavioral health or medicine approach to community health care, and it can result in a greatly expanded service delivery capacity as other staff are

trained to deliver packaged programs. The linkage model promotes the use of population-based approaches and it not only links, but integrates the treatment strategy of a variety of participating agencies. Needless to say, we should study the Linkage Mental Health Worker concept, because it perhaps could be adopted for the substance abuser, and it may be the most cost effective approach currently available to us.

DISCUSSION SUMMARY

Fred Altman, Ph.D., and Sidney H. Schnoll, M.D.

The primary focus of this discussion was on aftercare services. Former drug abusers often experience greater discrimination in obtaining these services than patients with other psychiatric illnesses or alcoholism. There was considerable discussion but no agreement on the relationship between the lack of aftercare and recidivism.

The negative attitude toward methadone in many communities was also discussed. A supportive community was considered to be especially important for methadone patients who drop out of treatment prematurely. However, it was felt that community attitudes towards methadone are often adopted by patients themselves, causing them to terminate treatment prematurely. Thus, the negative community attitude serves both to deprive the patients of the treatment and the support they especially need. Furthermore, a supportive community was considered particularly important when direct services are limited. However, it was felt that the negative community attitudes toward methadone, especially in these days of declining funding, contribute to a loss of services for methadone patients. Thus, again the negative attitude towards methadone leads to the loss of services for the patients and the support they especially need.

The lack of community support, especially the resulting loneliness, was thought to contribute to many methadone patients and former patients reinitiating contact with their drug using peers. The reestablishment of these relationships usually leads to the return to drug use. In this regard the "chicken and egg" problem was discussed. Is the decision to return to drug use made, albeit unconsciously, when the individual reinitiates relationships with drug using peers?

To improve aftercare services, methadone programs could do the following: 1) establish aftercare coordinators to work closely with patients and link them to the appropriate community services; 2) encourage the development of volunteer programs where the volunteers can act as role models and assist integration to a non-drug using culture; 3) be sensitive to the community needs in setting up vocational programs; and 4) encourage the development and use by patients of self-help programs in the community.

There was speculation about why Narcotics Anonymous (N.A.) has not been more successful. Among the reasons mentioned were: 1) N.A. has not been around long enough; 2) professional treatment services are free for narcotic addicts and this is in competition with N.A.; 3) many of the former addicts who might have formed the leadership for N.A. chapters found compensated employment in treatment programs and consequently did not have time for or have an interest in N.A.; and 4) there are possible significant differences in personalities and socioeconomic variables between narcotics addicts and the kind of individuals who started and make up Alcoholics Anonymous.

CHAPTER 6. AN OVERVIEW OF CLIENT CHARACTERISTICS, TREATMENT SERVICES, AND DURING-TREATMENT OUTCOMES FOR OUTPATIENT METHADONE CLINICS IN THE TREATMENT OUTCOME PROSPECTIVE STUDY (TOPS)

Robert L. Hubbard, Margaret Allison, Robert M. Bray, S. Gail Craddock, J. Valley Rachal

and

Harold M. Ginzburg

INTRODUCTION

Drug abuse treatment in the United States has evolved rapidly over the past decade. Both the types of clients entering treatment and the nature of treatment services have changed in many important ways (Jaffe 1979). Only two studies are available that provide data on both these topics for national samples of drug treatment clients: the Drug Abuse Reporting Program (DARP) and the Treatment Outcome Prospective Study (TOPS).

DARP Research

The first comprehensive data at a national level were gathered from 1969 to 1973 in the Drug Abuse Reporting Program (DARP). In the DARP research, baseline and in-treatment data were collected on over 44,000 clients who entered drug abuse treatment programs (Sells 1974; Sells and Simpson 1976), and follow-up interviews were conducted for these cohorts approximately 5 years after clients began treatment. But even the data from DARP are somewhat limited for current policy and program purposes. There have been rapid changes in drug abuse problems, the nature, funding, and availability of treatment services, and the clients who seek treatment since the last DARP cohort entered treatment in 1972-73. Consequently, there are

many unanswered and important questions about the backgrounds of clients who enter treatment, the nature, effects, and quality of the services provided and rceived, and the changes in behavior that occur both during and after treatment.

TOPS Research

Much of the information on these questions needed by policymakers, practitioners, and researchers can be provided by the Treatment Outcome Prospective Study (TOPS). Funded by the National Institute on Drug Abuse (NIDA) in cooperation with the National Institute of Justice (NIJ), this research is aimed at providing timely data on treatment currently provided to individuals with drug problems. TOPS is a long-term, large-scale longitudinal investigation of the natural history of drug abusers who have sought services in federally funded drug abuse treatment programs. This research tracks a multi-year census (1979-1981) of persons identified as eligible for treatment at selected drug treatment programs and by the Treatment Alternatives to Street Crime (TASC) programs.

The treatment programs and individual clients have voluntarily participated in the study. Program researchers, hired and trained specifically for TOPS, were assigned to interview the clients. Demographic and baseline behavioral data were collected at the time the client sought admission to the treatment program. At months 1, 3, and quarterly thereafter, for up to 2 years while the client remained in treatment, additional indepth assessments of behavior, attitudes, and treatment processes were conducted. These assessments were continued in the post-treatment period by follow-up interviews at 3 months, 1 year, and 2 years after termination.

In addition to providing an overall perspective on the major types of drug treatments available in the United States, TOPS provides indepth information on the characteristics and behaviors of clients, and the various outcome behaviors during and after treatment.

The TOPS data base for this paper includes the questionnaire responses of the directors of 15 methadone clinics, personal interviews at admission and during treatment with 1,112 clients entering methadone treatment in 1979 and 1,548 clients entering treatment in 1980, and abstractions

of clinical/medical records for a sample of 349 of these clients.

Purpose and Overview of This Paper

The purpose of this paper is to present some TOPS data that can be used to provide detailed, up-to-date information on methadone clients and treatment. In the paper we provide data on TOPS methadone programs and clients and a brief description of the nature of TOPS data and the generalizability of TOPS results to outpatient methadone treatment throughout the United States. Although we highlight some key elements of the TOPS data, more indepth examinations of the data have been and are being conducted. The data we present here are descriptive and form the basis for generating hypotheses to direct future, more comprehensive analyses. These analyses can provide information to help address some of the complex and controversial issues relating to providing effective and efficient outpatient methadone treatment.

In the first section of this paper we outline some of the issues previously raised in the literature and in this monograph on methadone treatment that can be examined in the TOPS data. After a brief discussion of the methods used in the study, we present data in three major areas: client characteristics, treatment services, and during treatment outcome behaviors. We describe the characteristics of TOPS clients who entered methadone treatment and, where possible, comparisons are made with the client sample in the DARP research and Client Oriented Data Acquisition Process (CODAP) data. The next section of the paper briefly describes the nature of treatment available in outpatient methadone programs in 1979 and 1980 and the treatment services provided to individual clients. Finally, we present data describing the behavior of clients during their first 6 months in treatment. We then summarize the results of these analyses and present recommendations of issues that appear to warrant further examination.

REVIEW OF MAJOR ISSUES IN OUTPATIENT METHADONE TREATMENT

In the 1960s, Dole and Nyswander (Dole and Nyswander 1965; Dole et al. 1968) demonstrated that serious, long term opiate addiction could be treated successfully with a daily oral dose of methadone. As a result of this work, a

methadone maintenance program was opened at Beth Israel Hospital in New York. The apparent success of this program led to the establishment of others. By the early 1970s, it was an accepted mode of treatment for opiate abuse regulated jointly by the Food and Drug Administration and the National Institute on Drug Abuse (U.S. Department of Health, Education, and Welfare 1977; U.S. Department of Health and Human Services 1980). The number of methadone maintenance clinics increased rapidly between 1970 and 1973, and by the late 1970s over 75,000 addicts were being treated in methadone maintenance treatment programs across the United States (Lowinson and Millman 1979).

Objectives and Approaches of Methadone Treatment

The regulations that governed federally supported methadone treatment programs through 1981 specified certain admission, service, and documentation requirements. Briefly, each program was required to obtain a personal and medical history for each client and to ensure that the client met the guidelines for admission to treatment. The programs were also to provide a comprehensive physical examination including any lab or special exams indicated in the judgment of the attending physician. In addition, regulations defined maintenance treatment as that in which methadone is administered to a drug dependent individual at relatively stable dosage levels for a period in excess of 21 days as an oral substitute for heroin or other morphine-like drugs (U.S. Department of Health and Human Services 1980). Methadone maintenance treatment is to be provided in conjunction with provision of appropriate social and medical services. Clearly, after stabilization, social rehabilitation is an important goal of methadone maintenance treatment.

The approaches taken by programs after stabilization might be categorized on the basis of two main issues: the emphasis on supportive services and the orientation toward abstinence. Although all programs attempt to provide some supportive services, the level of provision and the support for specific services vary from program to program. From the beginning, Dole and Nyswander (1965) have held that supportive social services such as psychotherapy, vocational training, and educational programs are an essential part of treatment. In his comprehensive book on methadone maintenance, Newman (1977) agrees that methadone by itself cannot be a complete treatment for heroin addiction but also points out that the kinds of services needed

and the special role of psychological services are still debatable. Lowinson and Millman (1979), discussing the characteristics of good methadone maintenance programs and the various services which should be included in them, assert that "severe social and psychological disability is frequently a product of the drug-dependent life," and appropriate services are necessary to overcome these disabilities.

Graff and Ball (1976) discuss two models of methadone treatment. The authors refer to these models as the "metabolic" and the "psychotherapeutic." According to the metabolic model, drug abuse is primarily a medical problem which can be alleviated chemically by the use of a daily dose of methadone. Once the medical problem is solved, the patient is free to work on solving his or her secondary problems, namely maladaptive behavior patterns. Methadone is viewed in much the same way as insulin is for the diabetic, and abstinence is not an important goal of treatment. Psychotherapy, if included at all, is an adjunct. In the psychotherapeutic model, the emotional disorder is presumed to be primary, and drug abuse is seen as a symptom or manifestation of it. Chemicals such as methadone are considered to be an adjunct to the principal (psycho)therapy in this model. Methadone is viewed as a helpful crutch to be used until the psychotherapy is successful in alleviating the emotional distress which is assumed to be the underlying cause of the client's drug abuse. At that time, detoxification from it is encouraged. Eventual abstinence from all drugs, including methadone, is usually an important goal of treatment within this model.

McLellan et al. (1982), in a study of over 600 drug abusers treated in six different treatment programs, have shown that the severity of psychological symptoms was an important contributor to outcome in methadone maintenance programs. Woody et al. (1981), in their intensive study of a small group of methadone clients, recently found that the severity of psychological symptoms was highly correlated with several well known predictors of outcome including methadone dose, nonprescription drugs in urine tests, ancillary medicines prescribed in the clinic, and employment. It was found that the most symptomatic patients used more drugs (licit or illicit), worked less, and generally did worse than their healthier counterparts. Thus, this study supports the concept that the emphasis on supportive services, particularly psychological

services, may be essential to the successful rehabilitation of drug abuse treatment clients.

Within the TOPS data base are outpatient methadone programs that reflect this range of approaches to treatment. One objective in TOPS is to characterize treatment according to these general approaches and to examine specific issues related to effective treatment.

Major Issues

Outpatient methadone treatment has been and still is a controversial approach to treating heroin addiction. The various approaches that have been taken and advocated have raised a number of important issues, including detoxification from methadone as a treatment goal, dosage effects, and take-home policies. Some of the issues are discussed briefly in the following paragraphs in order to suggest important hypotheses for the analysis of the TOPS data and areas of investigation for other studies. In addition, these and other issues which are important to the understanding of methadone maintenance treatment are discussed in the papers by Woody and others in this volume.

Maintenance Versus Abstinence. Clearly, the controversy over methadone maintenance versus detoxification from methadone has implications for program planning, policy, services offered, treatment goals, definitions of success, funding and staffing of programs, and a myriad of other issues. The Federal regulations which governed methadone maintenance treatment did not necessarily support either position. They stated that "an eventual drug-free state is the treatment goal for many patients; it is recognized, however, that for some patients the drug may be needed for a long period of time" (U.S. Department of Health and Human Services 1980).

The ambivalence expressed in the Federal regulations has been reflected in the programs themselves. Levine and Kabat (1975) interviewed clients in a methadone treatment program and found that, while clients were quite aware of all the rules regarding the use of methadone, they did not understand the overall treatment plan or program goals.

Several researchers have carried out follow-up studies of methadone maintenance clients (Cushman 1977; Dole and

Nyswander 1976; Gearing 1971, 1972; Riordan et al. 1976; Sells 1977) and generally report more favorable results for clients remaining in treatment. Cushman (1977) and Newman (1977) both question the wisdom of the government policy of encouraging detoxification. Dole and Nyswander (1976) point out that many clients are refused supportive services once they have achieved detoxification--the period when they are most likely to need these services.

Dosage Effects. Several researchers have examined the effects of methadone dosage level. Handal and Lander (1976) found that initially higher doses were associated with less illicit drug use, but that the longer the clients remained in treatment, the more effective lower dosage levels were in curbing illicit drug use. Siassi et al. (1977) reported that higher (86 mg/day) doses were related to successful treatment outcome while lower (48 mg/day) dosage levels were associated with treatment failures. McGlothlin and Anglin (1981) also found that high dose (80-100 mg/day) clients fared significantly better than low dose (40 mg/day or less) clients. Goldstein (1971), on the other hand, found that dosage level (30-200 mg/day) had little effect on a number of measures such as urine tests, clinic attendance, and employment. He also reported that higher dose clients tended to experience more undesirable side effects, such as constipation and impotence. Crowley and Simpson (1978) similarly found that high doses of methadone may have deleterious effects on sexual functioning. Havassy and Hargreaves (1979) studied the effects of self-regulation on clients' behavior. They found that clients who had the privilege of self-regulation used higher dose levels than clients in the control group, but that, at the same time, their use of illicit drugs was significantly less than the controls.

Take-Home Policy. Little work on this issue has been reported. Stitzer (1977) studied the use of take-home privileges as a reinforcement for attendance at counseling sessions. She found that attendance increased significantly above the levels observed during the period of noncontingency. Likewise, Milby et al. (1978) concluded that methadone take-home privileges can be powerful reinforcers of rehabilitative behaviors.

Urinalysis Monitoring. Monitoring of illicit drug use by means of urinalysis has been a common practice in most drug treatment programs since their inception. Whether such monitoring affects the clients' behavior, attitude

toward treatment, or treatment outcome has apparently not been studied. Goldstein et al. (1977), however, have examined whether onsite testing with immediate feedback of results might have some therapeutic value. They concluded that the onsite urinalysis had no therapeutic advantage over the usual offsite testing. They also reported negligible differences in illicit drug use between the onsite test and offsite test groups.

Counselor Characteristics. The type of counselor is another factor in treatment whose impact on outcome is not well understood. Brown and Thompson (1973) reported no significant differences in the outcomes of clients treated by exaddicts as opposed to professional counselors in methadone programs. They used a variety of outcome measures including average length of stay in treatment, percent completing treatment, percent arrested, average number of arrests, and percent employed. Longwell et al. (1978) investigated the effect of counselor type on outcome in 253 patients in a methadone maintenance program. In this study, clients were evaluated over four 3-month periods, and outcome was measured by patient urinalysis for heroin use. The results showed no significant differences among patients with the following counselor types: (1) multiple exaddict (EA) counselors; (2) multiple nonaddict (NA) counselors; (3) EA counselors followed by NA counselors, or vice versa; (4) single EA counselor; or (5) single NA counselor. The data also showed that clients who had no counselor for one-third or more of each 3-month period had a higher percentage of urines positive for heroin.

LoSciuto et al. (1979) investigated the outcome effects of three types of counselors working in drug-abuse treatment programs: (1) professional counselors who held at least a bachelor's degree and who did not have addiction histories; (2) exaddict paraprofessionals who usually did not hold a bachelor's degree; and (3) paraprofessionals who had neither a bachelor's degree nor an addict background. Data were collected from methadone maintenance and drug free program clients in five major cities. Clients' progress toward achieving treatment goals while in treatment was not related to counselor type.

Retention. The studies by Siassi et al. (1977) and McGlothlin and Anglin (1981) suggest that retention in methadone maintenance treatment programs may be positively related to dosage level. These authors also report that high dose, long-term methadone maintenance

clients show substantially fewer arrests, less time incarcerated, and less readdiction than low dose, short-term clients.

Other recent research suggests that a broad definition of retention may be needed. Simpson et al. (1978) reported that 39 percent of methadone maintenance clients return to treatment within a year. This raises the question of whether repeated exposures to treatment are more effective than one episode (McLellan and Druley 1977). Using CODAP data, Siguel and Spillane (1978) argue that this is not the case. Clients reporting no previous treatment experiences in CODAP have a greater likelihood of completing treatment. Because of the limited background data available in CODAP, it was not possible to adjust for other factors that might have influenced the probability of completing treatment. However, Simpson et al. (1978) report a similar result in th DARP follow-up. Thus, the total time in treatment appears less important than the retention in a single program. Retention in a single program was identified as a key correlate of successful behaviors across a variety of indices and types of programs, even after controlling for other factors (Simpson et al. 1978).

Reintegration into the Community. Cushman (1977) found that clients who remained in treatment formed a distinct subculture associated with neither the drug subculture nor the "straight" society. About half of them received some support, including payment for their methadone treatment, through the welfare system, although there was a trend toward greater self-sufficiency over time. These clients were physically less healthy than the general population but much better off than untreated addicts. Cushman argued that one of the reasons for the formation of the subculture was the prejudice of the general public against such former addicts. Preble and his colleagues (Preble and Casey 1969; Preble and Miller 1977) described the daily lives of methadone maintained exaddicts who have not been reintegrated into society and who adopt a lifestyle characterized by "methadone, wine, and welfare."

The TOPS research program includes data that can be used to provide information on some of the major aspects of each of these issues for a heterogeneous national sample of methadone programs and clients. The TOPS follow-up data will allow us to describe outcomes for clients maintained on methadone and those who have been detoxified.

Information on dosage effects, take-home policy, urinalysis monitoring, and counselor characteristics is available from the clinical/medical record abstractions. Retention and community integration both during and after treatment are two outcome variables that are examined in detail. In TOPS, comprehensive, systematic assessment of all these issues can be conducted. With multivariate analytic techniques it will be possible to describe relationships among client characteristics, treatment services, and outcomes. Furthermore, we can examine the relative impact of any one or a combination of variables on outcomes. The data presented in the following section outline the types of information available in TOPS that can be used in such analyses.

METHODOLOGY

This section describes the general methodology of the TOPS research program. More complete information about the technical issues and details is reported by Hubbard et al. (1982). In addition, Bray et al. (1981) and Craddock et al. (1982) provide descriptive reports of the 1979 and the 1980 cohorts, respectively. The following section describes the major elements of the TOPS research design, the selection of communities, programs, clients, and clinical/medical records for the study, and the instruments used to collect comprehensive information on treatment process.

Selection of Communities, Programs, Clients, and Clinical/Medical Records

Each of the TOPS admission cohorts (1979-1981) consisted of all clients who applied for treatment or were admitted to selected drug treatment programs in 10 cities. Major emphasis was placed on a reasonable, manageable number of selected programs in order to tightly control the study, to minimize nonresponse, and to maximize quality control. The programs considered for selection in each city included the major modalities of detoxification, outpatient methadone, residential, and outpatient drug free.

Sample of Communities. Communities were selected by region to provide a geographical distribution of the programs and treatment systems studied. Community selection included consideration of the stability of the treatment

system and the environment in which the program functioned. Based on considerations of the technical, administrative, and logistical advantages and disadvantages of working in each city, the final sample for the 1979 Intreatment Study included the cities of Chicago, Illinois; Des Moines, Iowa; New Orleans, Louisiana; New York, New York; Phoenix, Arizona; and Portland, Oregon. For the 1980 admission cohort, additional cities and programs were considered to maximize the number of outpatient drug free programs and provide a large sample of nonopiate, multiple drug abusing clients. Based on the SMSA data from CODAP, programs in the two cities that best met these criteria--Miami, Florida and San Francisco, California--were added in January 1980. One outpatient methadone program was located in each city.

Sample of Programs and Clinics. The programs selected in each site included those that (1) represented major modalities, (2) were established, functioning programs, and (3) reflected particular typologies of treatment. While it is clear that the programs specially selected for TOPS do not constitute a statistically representative sample, they do reflect a variety of approaches to treatment. Efforts were made to select programs that reflected typical approaches to major modalities of treatment, as well as variations in those approaches. Eight outpatient methadone programs, which dispensed methadone and services at 15 different clinics, were included in the 1979 study. In the second year (1980), two more methadone programs with three clinics were added to the study. Descriptions of 15 clinics were obtained from the clinic directors. Clinical/medical record abstractions and client interview data were also available for 15 clinics. Two clinics closed before descriptions and abstractions could be collected.

Sample of Client Interviews. The Intreatment Study employed a census rather than a sample of clients in each participating methadone program. An attempt was made to interview all drug abusers when they first physically contacted the treatment program to gain admission. Individuals clearly not eligible for a drug treatment program were, of course, not interviewed for the TOPS Intreatment Study. For example, alcoholics with no drug problem, individuals with overriding psychiatric problems, and those not meeting any program eligibility criteria such as age, drug history, or involvement with the criminal justice system were excluded. The 1979 cohort consisted of 1,112

clients, and the 1980 cohort included 1,548 clients. Descriptive data on the characteristics of clients in the third section of this paper, and during-treatment outcomes in the fifth section, are based on interviews with these clients.

Sample of Clinical/Medical Records. Clinical/medical records were abstracted for a sample of clients participating in the TOPS Intreatment Study who were selected for the TOPS Followup Study. All clients selected for the TOPS Followup Study and who remained in treatment 3 months or more were included in the clinical/medical record abstraction. A 10 percent sample of clients selected for the Followup Study who remained in treatment less than 3 months was also selected. Thus, complete intake interview, intreatment interview, treatment record, and follow-up interview data will be available for a large proportion of clients staying in programs at least 3 months.

Clinical/medical record abstractions for a total of 349 clients in 15 methadone clinics were obtained. Self-report data from the 3-month intreatment interview were appended to the data file for the clinical medical record information.

Instruments and Data Collection Procedures

The treatment process study is based on data from three sources: the treatment directors of the programs, the clients' records kept by the programs, and the clients themselves. Client self-report data were taken from the TOPS intake and 3-month intreatment interviews. In addition, two data collection instruments were especially designed and used to gather treatment process information from the client files and from treatment staff in TOPS programs. These two instruments are referred to as the Clinical/Medical Record Review Form and the Director/Counselor Checklist, respectively.

TOPS Intreatment Interview Forms. As mentioned earlier in this report and detailed in Hubbard et al. (1982), the TOPS clients were interviewed by specially trained program researchers at intake, 1 month, and 3 months after admission, and quarterly thereafter for up to 2 years if they remained in treatment. These interviews were designed to gather a wide variety of information on client characteristics (age, sex, prior treatment, ec.), client

behaviors (drug use, criminality, employment, etc.), and treatment received (counseling, services, etc.).

Clinical/Medical Record Review Form. The Clinical/Medical Record Review Form was designed to enable specially trained abstractors to gather information from client files on a variety of topics relevant to treatment process. Sociodemographic information as well as data on services received, treatment plans, drug use, medications prescribed, treatment history, and follow-up services were obtained, to the extent possible, from the program records from the sample of clients from the 1979 and 1980 cohorts. Many of the data items were based on CODAP reports. Other items required a review of the clinical/medical file and a coding of the information in the file.

Director/Counselor Checklist. This checklist was designed to be filled out by the director of treatment and two or three counselors at each clinic. Topics covered include program policy and philosophy, approach to treatment, emphases and goals for treatment, size of the program, caseload per counselor, services provided at the program or through referral, criteria for completion of program and for discharge from program, and many other relevant topics to the study of treatment process.

The checklist was designed so that the data collected with it could be integrated with the treatment process data from the other two sources. Data from the three other sources could be compared and used to describe the programs and the process of treatment within and across those programs.

CLIENT CHARACTERISTICS

The first section presents a general description of demographic characteristics, treatment experience, characteristics of drug abuse, and other problems for the TOPS 1979 and 1980 admission cohorts based on information drawn from the TOPS intake interview. The data enable us to compare and contrast the characteristics and behaviors of the TOPS sample with those of similar types of drug treatment clients and persons with similar backgrounds not in treatment. These basic variables also provide a set of covariates that must be taken into account in the multivariate assessment of treatment outcomes. Where possible, comparisons are made between the TOPS, DARP, and CODAP data sets. More comprehensive reports on the

1979 TOPS admission cohort (Bray et al. 1981) and the 1980 TOPS admission cohort (Craddock et al. 1982) are also available

Demographic Characteristics

In table 1, data on sex, age, and race/ethnicity of TOPS, DARP, and CODAP clients are presented. About 30 percent of clients in TOPS and CODAP outpatient methadone programs are female, a higher proportion than was reported in methadone programs in DARP.

The clients in outpatient methadone programs tend to be older than clients in other modalities/environments, as might be expected due to the admission criteria. However, despite the recent lowering of the minimum age for admission from 21 to 18, the TOPS and CODAP clients are older than DARP clients. In DARP, 48 percent of the clients were 25 years old or less. In TOPS only about one-fourth of the clients are under 25. CODAP uses slightly different age categories (18-19, 20-24, 25-29, 30 and over), which would appear to account for differences between TOPS and CODAP samples.

A major difference between DARP and TOPS is the higher proportion of non-Hispanic white clients in TOPS. More than 40 percent of the clients in TOPS outpatient methadone clinics are non-Hispanic white compared to only 16 percent in the DARP sample. The TOPS data also differ from the CODAP data in the proportion of Hispanic clients. TOPS programs had over 20 percent Hispanic compared to 11 percent in CODAP programs.

These results clearly show that the demographic characteristics of clients now entering methadone programs have changed greatly from those of clients interviewed in the DARP research. Both the TOPS and CODAP data confirm these differences. The findings also indicate that except for a higher proportion of Hispanics in the TOPS data, the TOPS sample of clients generally reflects the type of client entering outpatient methadone clinics in 1979 and 1980. This strongly suggests that the conclusions generated from the TOPS data can be appropriately applied to outpatient methadone treatment in general.

Table 1. Demographic characteristics at intake of DARP (1969-1973), TOPS (1979-1980), and CODAP (1979-1980) outpatient methadone program clients

	DARP	TOPS		CODAP	
	1969-1973 (N=11,023)	1979 (N=1,112)	1980 (N=1,548)	1979 (N=23,579)	1980 (N=27,571)
Demographic characteristics					
Sex					
Male	78.0%	71.7%	67.5%	69.5%	69.5%
Female	22.0%	28.3%	32.5%	30.5%	30.5%
	100.0%	100.0%	100.0%	100.0%	100.0%
	(N=11,023)	(N=1,112)	(N=1,548)	(N=23,455)	(N=27,667)
Age					
Under 20	13.0%	3.1%	1.9%	0.6%	0.3%
21-25	35.0%	23.6%	20.3%	15.5%	11.6%
26-30	22.0%	38.0%	39.1%	40.3%	38.3%
Over 30	22.0%	35.3%	38.7%	43.6%	49.8%
	100.0%	100.0%	100.0%	100.0%	100.0%
	(N=11,023)	(N=1,111)	(N=1,547)	(N=23,498)	(N=27,649)
Race/ethnicity					
White	16.0%	43.5%	43.4%	46.3%	45.5%
Black	58.0%	35.6%	32.5%	42.1%	42.8%
Hispanic	25.0%	20.7%	22.9%	11.0%	11.3%
Other	1.0%	0.2%	1.2%	0.6%	0.4%
	100.0%	100.0%	100.0%	100.0%	100.0%
	(N=11,023)	(N=1,111)	(N=1,548)	(N=23,486)	(N=27,746)

Treatment Experience

Table 2 presents data on the number of prior treatment experiences of clients and their legal status at admission. In comparing clients entering CODAP and TOPS programs to the DARP sample, we also find that clients in the recent data sets had more experience with treatment, and DARP clients were less likely to be involved in the criminal justice system at the time of admission.

Over half the DARP methadone clients had no prior treatment episodes, but over 70 percent of the TOPS clients and 80 percent of the CODAP clients had previously been in treatment. About one in four TOPS clients had five or more prior treatment episodes. This result is consistent with the finding that TOPS and CODAP clients tend to be older than those in the DARP sample. The major difference between TOPS and CODAP is that TOPS clients report more previous episodes. This may be due in part to the more detailed series of questions on prior treatment used in the TOPS intake interview.

Where 30 percent of the DARP clients reported some kind of legal status at their admission to the DARP program, only a little over 16-17 percent of TOPS clients reported such involvement. More DARP clients appeared to be on probation or awaiting trial. The criminal justice system may have had a more positive attitude toward methadone in the early 1970s than is evident today. We found that few TOPS clients were referred to methadone programs through the criminal justice system (Collins et al. 1982).

Drug Use and Related Problems

Drug abuse patterns of methadone program clients appear to have changed dramatically over the past decade. Because of the more comprehensive assessment of drug use in the TOPS research, direct comparisons made with the DARP may be misleading. It is clear, however, that a higher proportion of TOPS clients are more likely to use a large variety of drugs and use them more frequently than DARP clients. In table 3 we see that over a quarter of the TOPS methadone clients had used cocaine and minor tranquilizers weekly in addition to heroin and other narcotics. Over half also use marijuana weekly or more often. In more detailed analyses which are not presented in

Table 2. Number of prior treatment experiences and legal status at admission for DARP (1969-1973), TOPS (1979-1980), and CODAP (1979-1980) outpatient methadone program clients

	DARP	TOPS		CODAP	
	1969-1973 (N=11,023)	1979 (N=1,112)	1980 (N=1,548)	1979 (N=23,579)	1980 (N=27,571)
Number of prior treatment experiences					
None	51.0%	29.7%	23.9%	17.3%	18.3%
One	24.0%	16.2%	16.8%	22.6%	22.7%
Two	12.0%	13.3%	13.4%	19.9%	20.4%
Three	5.0%	10.6%	11.3%	15.1%	14.8%
Four	3.0%	6.7%	8.0%	9.7%	8.9%
Five or more	5.0%	26.6%	26.6%	15.4%	14.9%
	100.0%	100.0%	100.0%	100.0%	100.0%
	(N=10,909)	(N=1,073)	(N=1,510)	(N=23,378)	(N=27,596)
Legal status					
Probation	12.0%	5.3%	7.4%	NA	NA
Parole	5.0%	6.0%	5.6%	NA	NA
Awaiting trial	11.0%	3.4%	3.3%	NA	NA
Other	2.0%	1.3%	0.6%	NA	NA
None	70.0%	84.0%	83.1%	NA	NA
	100.0%	100.0%	100.0%		
	(N=10,968)	(N=1,104)	(N=1,543)		

table 3, over half of the TOPS clients were classified as moderate or heavy drinkers, and very few were found who had used heroin exclusively in the year prior to treatment.

Table 3. Weekly or more frequent alcohol or nonmedical drug use in year preceding treatment by TOPS (1979-1980) outpatient methadone program clients

	TOPS admission cohort	
	1979 (N=1,112)	1980 (N=1,548)
Drug type	(Multiple responses permitted)	
Alcohol	45.2%	48.0%
Marijuana	61.4	54.4
Inhalants	0.5	1.3
Hallucinogens	1.2	2.0
Cocaine	25.0	29.2
Heroin	63.3	64.4
Methadone	19.9	19.7
Other narcotics	25.7	27.6
Minor tranquilizers	28.2	23.2
Major tranquilizers	1.4	1.2
Barbiturates	8.2	5.1
Sedatives	4.3	6.5
Amphetamines	14.3	7.2

Table 4 shows a typology developed to classify patterns of use (Bray et al. 1982). From this table it is clear that methadone clients use a variety of drugs. Even those who can be labeled heavy heroin users also report frequent use of cocaine, marijuana, and alcohol. These results suggest that if the stereotypic "junkies" or "addicts" of the early 1970s exist, they are not entering methadone clinics. Because current clients use multiple drugs, they may be more difficult to treat.

Table 4. Patterns of drug use in the year prior to treatment by TOPS (1979-1980) outpatient methadone program clients

	TOPS admission cohort	
	1979 (N=1,112)	1980 (N=1,548)
Drug type		
Heavy heroin and/or opiate use with multiple (3 or more) nonopiate use	42.1%	41.6%
Heavy heroin and/or opiate use with some (1-2) nonopiate use	11.2%	12.5
Heavy heroin use with cocaine, marijuana, or alcohol	20.1	23.8
Multiple (3 or more) nonopiate use	15.5	10.9
Other patterns	11.1	11.2
	100.0%	100.0%

Three-fourths of the clients entering the programs report having some type of drug related problem, as shown in table 5. The most common are family or financial problems. Between one-third and one-fourth of the clients report medical, psychological, or job/education problems.

Table 5. Types of drug related problems reported in the year prior to treatment by TOPS (1979-1980) outpatient methadone program clients

	TOPS admission cohort	
	1979 (N=1,112)	1980 (N=1,548)
(Multiple responses permitted)		
Type of drug related problem		
Medical	28.1%	32.8%
Psychological	35.4	33.2
Family	49.7	44.3
Legal	17.9	18.0
Job/education	29.3	24.0
Financial	57.3	64.2
No problems	24.1	20.5

Other Problem Behaviors

In addition to drug related problems in TOPS, we assessed a variety of behaviors that may indicate problems that could be affected by treatment programs. Three important problem areas appear to be mental health, criminal behavior, and employment. Problems in all these areas were evident for methadone clients, as can be seen in table 6.

Over half of the methadone clients report having exhibited some indicator of depression in the year before admission. Three in 10 have had suicidal thoughts or attempted suicide.

Many report involvement in illegal activity. However, the level of involvement appears to be less than that of treatment admission cohorts in the early 1970s. The TOPS

Table 6. Indicators of depression, involvement in illegal activity, and weeks of full-time employment in the year prior to treatment by TOPS (1979-1980) outpatient methadone program clients

	TOPS admission cohort	
	1979 (N=1,112)	1980 (N=1,548)
Drug type		
None	42.8%	43.6%
Could not get out of bed	27.4	
24.4		
Suicidal thoughts	24.2	25.8
Suicide attempts	5.6	6.2
	100.0%	100.0%
	(N=1,102)	(N=1,524)
Type of illegal involvements (Multiple responses permitted)		
None	56.3%	46.6%
Sale of illegal drugs	9.3	18.6
Forgery/embezzlement	5.7	6.9
Theft/larceny	10.8	15.4
Burglary	4.7	8.3
Robbery	3.7	6.6
Weeks of full-time (35+ hours) work		
None	43.4%	52.1%
1-13	9.9	9.7
14-39	19.4	17.1
40-51	8.0	7.1
52	19.3	14.0
	100.0% (N=1,097)	100.0% (N=1,519)

clients are older than DARP clients, have had more treatment experience, and use a variety of less expensive drugs that may substitute for heroin. Almost half were in treatment in the year prior to their admission to the TOPS program. These factors may have contributed to a lower level of involvement in illegal activity prior to their admission to the TOPS methadone programs.

About half of the methadone program clients report working not more than 35 hours in any week in the year prior to treatment. Although there are a substantial number of clients who report full-time work, employment continues to be a major problem area for methadone program clients.

These data indicate that, in addition to drug abuse, methadone clients have problems in a variety of areas. Clients with multiple drug abuse, combined with an array of other problems, may require more extensive services than clients entering the early methadone clinics. The next section of this paper discusses some of the services rendered to clients in the TOPS outpatient methadone clinics.

TREATMENT SERVICES

This section presents initial data on our attempt to describe treatment services offered in 16 outpatient methadone clinics participating in the TOPS study in 1979 and 1980. The director of one clinic did not respond, and clinical/medical record abstractions were not available for another clinic. In contrast to the preceding section, this section focuses on the clinics as the unit of analysis. The clinics were grouped by the typical number of clients enrolled: small (fewer than 200 clients), medium (200-300 clients), and large (more than 300 clients).

The data presented are obtained from questionnaires completed by clinic directors, abstractions of clinical/medical records for a sample of clients, and client self-reports in the TOPS in-treatment interview of services received.

In addition to describing treatment services currently available and received in methadone programs, subsequent analyses will summarize the information about services available and received to create a set of variables describing the nature of treatment. Selected variables will

be appended to client records in order to assess the impact of treatment variables on outcomes using multivariate analytic techniques such as multiple regression, path analysis, and LISREL.

Philosophy and Approach to Treatment

As previously noted, one of the major issues in methadone treatment is the question of abstinence or maintenance as the eventual goal of treatment. In table 7 the responses of clinic directors to a number of questions on this issue are presented. When asked to place their programs in either of the two categories of methadone programs proposed by Cole and James (1975), 11 chose the "change-oriented" category. This category emphasizes eventual drug free living as a major goal of treatment. The "adaptive" type of program would typically expect prescription of methadone indefinitely.

When asked directly how much their clinic encouraged long-term maintenance, only five clinic directors said maintenance was encouraged to a great or very great extent. Abstinence or detoxification from methadone was encouraged to a great or very great extent by 10 clinics.

The emphasis or major focus of counseling and therapy in most clinics was on practical problem solving for day-to-day living. A major focus on medical care was reported by only one clinic. Another reported its major focus was on changing the client's lifestyle through more intensive therapy.

Counseling

Another important aspect of treatment is the nature of counseling a client receives. As shown in table 8, there are various approaches to counseling available in methadone clinics. There is also great variation in the type and frequency of counseling offered in the clinics. Although all clinics report providing individual counseling, only half schedule it at least once a week with clients. Some form of group counseling is offered in 10 of the clinics. However, only four clinics typically schedule clients for group sessions at least once a week. The average caseload per counselor varies from less than 30 to over 50. As expected, the larger clinics report higher counselor caseloads. Exaddicts or peer counseling is used

Table 7. Type of program, encouragement of maintenance and abstinence, and focus of intervention in small, medium, and large TOPS outpatient methadone clinics as reported by clinic directors

	Clinic size			
	Small (200 clients) (N=4)*	Medium (200-300 clients) (N=6)	Large (300 clients) (N=6)	Total (N=16)*
Type of program				
Adaptive	1	2	9	12
Change oriented	2	4	5	11
Extent maintenance is encouraged				
Some	3	3	3	9
Great	0	3	1	4
Very great	0	0	1	1
Extent abstinence is encouraged				
Some	0	1	3	4
Great	3	4	1	8
Very great	0	1	1	2
Focus of intervention				
Physiological medical	0	0	1	1
Problem solving	2	5	3	10
Resocialization	0	0	1	1

*The director of one clinic did not respond.

Table 8. Average caseload per counselor, use of exaddict or peer counselors, the frequencies of group counseling and individual therapy or counseling sessions in small, medium, and large TOPS outpatient methadone clinics as reported by clinic directors

	CLINIC SIZE			
	Small (200 clients) (N=4)	Medium (200-300 clients) (N=6)	Large (300 clients) (N=6)	Total (N=16)
Average caseload per counselor				
20-29	2	1	0	3
30-39	0	2	1	3
40-49	1	1	0	2
50 or more	0	2	5	7
Use of exaddict or peer counselors				
Not at all	1	0	3	4
To some extent	0	6	2	8
To a great extent	2	0	0	2
To a very great extent	0	0	1	1
Frequency of group session				
None	0	3	2	5
Less than once a week	2	1	3	6
Once a week	1	1	1	3
More than once a week	0	1	0	1
Usual dose at admission (mg/day)				
0-24	3	3	3	9
25-49	0	3	1	4
50 or more	0	0	2	2

Table 8 (Continued)

	CLINIC SIZE			
	Small (200 clients) (N=4)	Medium (200-300 clients) (N=6)	Large (300 clients) (N=6)	Total (N=16)
Usual maintenance dose (mg/day)				
0-24	1	0	1	2
25-49	1	3	1	5
50 or more	1	3	3	7
Other drugs prescribed				
None	1	3	5	9
Tranquilizer	2	2	0	4
Antagonist	0	1	0	1

to at least some extent by most programs. Only four clinics report that exaddicts are not used in counseling clients.

Dosage Levels and Medication

The level of methadone dose at admission and for maintenance varies by clinic. Most of the clinics prescribe less than 25 mg/day at admission for the typical client. Two large clinics, however, report usual doses of over 50 mg/day at admission (table 9). The usual maintenance dose also varies. Half of the clinics reported usual maintenance doses of less than 50 mg.

Two small and three medium-sized clinics prescribed medication other than methadone. Four prescribed tranquilizers and one prescribed antagonists. The directors of large clinics all reported that no medication other than methadone was prescribed.

Table 9. Usual methadone dose at admission, usual maintenance methadone dose, and prescription of other drugs in small, medium, and large TOPS outpatient methadone clinics as reported by clinic directors

	Clinic size			
	Small (200 clients) (N=4)	Medium (200-300 clients) (N=6)	Large (300 clients) (N=6)	Total (N=16)
Usual dose at admission (mg/day)				
0-24	3	3	3	9
25-49	0	3	1	4
50 or more	0	0	2	2
Usual maintenance dose (mg/day)				
0-24	1	0	1	2
25-49	1	3	1	5
50 or more	1	3	3	7
Other drugs prescribed				
None	1	3	5	9
Tranquilizers	2	2	0	4
Antagonists	0	1	0	1

Types of Services

One of the important objectives of the TOPS treatment process study was to determine the types of services offered to clients in addition to treatment for drug abuse. We obtained data from two sources, the clinical/medical records and client interviews. Data from both sources are shown in table 10.

The clinical/medical records showed services received at any time in treatment. The client interview data were obtained after a client had been in treatment 3 months. We should expect that a higher rate of services would be reported in the clinical/medical records because they would typically cover a longer time period.

The data shown in table 10 are the percentage of clients receiving a service in each clinic. There is no weighting of clinics according to the number of clients in the clinic. There was substantial variation among clients in the percentage of clients receiving services. While the percentages receiving services may give an overall picture of services delivered, a measure summarizing the pattern and extent of services available in a clinic may be more useful.

Despite the limitations of the data, we can see a general picture of the types of services reported in the clinical/medical files. Most clinics do provide medical services to most of their clients. Psychological services are also provided. Other services are not generally offered by smaller clinics, and even in the clinics that do provide such services, only a small proportion of clients receive them.

Clients, as expected, report a lower level of services. Overall less than 10 percent of the clients in treatment for 3 months report receiving any services other than medical or psychological.

DURING-TREATMENT OUTCOMES

A variety of behaviors can be viewed as treatment outcomes. In TOPS we have examined five main outcome variables: use of primary drug, drug related problems, indicators of depression, commission of serious crimes, and full-time employment. In table 11 we present data on these measures in three time periods: before treatment,

Table 10. Average percentages of clients receiving seven types of services as reported by clients and as abstracted from clinical/medical records for small, medium, and large TOPS outpatient methadone clinics

	Clinic size			
	Small (200 clients) (N=4)	Medium (200-300 clients) (N=6)	Large (300 clients) (N=6)*	Total (N=16)*
	(Multiple responses permitted)			
Clinical/medical record of service at any time during treatment				
Medical	99%	58%	53%	67%
Psychological	35	30	24	29
Family	4	15	17	13
Legal	19	4	9	10
Education	0	10	18	10
Employment	8	23	31	22
Financial	0	10	35	16
Client self-report of service in the first 3 months of treatment				
Medical	30%	29%	46%	35%
Psychological	33	21	5	19
Family	15	8	3	8
Legal	4	5	3	4
Education	1	6	10	6
Employment	10	8	7	9
Financial	7	4	11	7

* Clinical/medical record data from one clinic had been abstracted but were not available when this paper was prepared.

Table 11. TOPS (1979-1980) outpatient methadone program clients reporting drug use, drug related problems, indicators of depression, commission of serious crimes, and full-time employment before and during treatment

	TOPS admission cohort	
	1979	1980
Weekly or greater use of primary drug		
Year before treatment	79.2%	83.7%
First 3 months in treatment	9.5	15.9
Second 3 months in treatment	8.6	15.4
Drug related problems		
Year before treatment	80.9%	78.8%
First 3 months in treatment	27.9	21.8
Second 3 months in treatment	22.4	17.6
Indicators of depression		
Year before treatment	57.8%	59.2%
First 3 months in treatment	31.1	28.7
Second 3 months in treatment	27.4	31.1
Commission (mean number) of serious non-drug defined crimes		
Year before treatment	21.9% (3.1)	26.5% (3.7)
First 3 months in treatment	11.31 (1.2)	122.0 (0.8)
Second 3 months in treatment	8.9 (0.6	8.9 (0.8)
Full-time employment at least 75% of the time		
Year before treatment	27.8%	19.6%
First 3 months in treatment	27.8	21.9
Second 3 months in treatment	31.0	22.5

during the first 3 months (intake to 91 days) in treatment, and during the second 3 months (92-182 days) in treatment. The same sample of clients, those who stayed in treatment at least 6 months, is used for the computations of percentages for each time period.

As can be seen in the table, all the outcome measures show improvement. There is a dramatic drop after 3 months in treatment in the percentage of clients using their primary drug on a weekly basis--from about 80 percent before coming to drug treatment to a little over 13 percent. Where eight of 10 clients reported a drug related problem in the year prior to treatment, less than three of 10 report any problems in the 3-month periods during treatment. There are fewer reports of depression.

Criminal behavior is reduced both in terms of the percentage of clients committing crimes and the number of crimes committed. The proportion of clients reporting full-time employment is slightly higher during treatment.

Taken together, these results show that impressive changes in behavior occur during methadone treatment. In order to better understand the nature, extent, and reasons for the changes, an important next step in the analysis plan for TOPS is assessing the impact of treatment and/or the elements of treatment on these outcome behaviors.

SUMMARY AND CONCLUSIONS

This paper has presented data and a brief discussion of the data to illustrate the utility and generalizability of the TOPS research program in addressing a variety of important issues concerning effective and efficient outpatient methadone treatment. The major issues on which analyses can be conducted include (1) the general objectives and approaches of treatment, particularly supportive services, (2) the orientation toward maintenance and abstinence, (3) dosage effects, (4) take-home policies, (5) urinalysis monitoring, (6) counselor characteristics, (7) retention in treatment, and (8) reintegration into the community.

The TOPS data base includes a large, heterogeneous, national sample of outpatient methadone clients and clinics. Questionnaire reponses are available from directors and counselors for 15 clinics. Personal interviews at admission and during treatment were conducted with 1,112

clients entering these outpatient methadone clinics in 1979 and with 1,548 clients entering treatment in 1980. Abstraction of clinical/medical records was completed for a sample of 349 of these clients.

Data from TOPS were presented and discussed on three topics: client characteristics, treatment services, and drug treatment outcome behaviors. The results of these analyses are summarized in the following paragraphs.

Outpatient methadone treatment programs in 1979 and 1980 served a heterogeneous client population that differed greatly from that served by programs in 1969-1973 as reflected by DARP. Specifically, the TOPS sample compared to the DARP sample has higher proportions of clients who

- are female (31 vs 22 percent);
- are over 25 years of age (76 vs 52 percent);
- are non-Hispanic whites (43 vs 16 percent);
- have had prior treatment experiences (73 vs 49 percent);
- have no involvement in the legal system (83 vs 70 percent); and
- use a variety of other nonopiate drugs, especially alcohol, marijuana, and cocaine.

The similarity of TOPS and CODAP client characteristics suggest that results from TOPS can be applied to the general population of outpatient methadone treatment clients.

For the year prior to entering TOPS outpatient methadone programs, clients reported

- weekly or greater nonmedical use of a variety of drugs, including alcohol (47 percent), marijuana (57 percent), cocaine (27 percent), and minor tranquilizers (25 percent);

- drug related problems in a variety of areas, including financial (61 percent), family (47 percent), mental health (34 percent), and medical (31 percent); and

- other problem behaviors such as indications of depression (57 percent), involvement in illegal activities (52 percent), and not working a full-time job (48 percent).

These reports indicate that, in addition to heroin and/or opiate addiction, clients have problems in a variety of areas. The array of problems, coupled with the abuse of multiple substances, suggests that current methadone programs may face a more difficult rehabilitation task than the early methadone clinics.

The approaches to treatment and the services offered vary greatly among clinics.

- Most of the 15 outpatient methadone clinics in TOPS seem to emphasize eventual drug free living (N=11), detoxification from methadone (N=10), and practical problem solving for day-to-day living (N=10)

- Individual counseling is used by all clinics. However, only half of the clinics report scheduling appointments once a week.

- Exaddicts or peer counselors are used at least to some extent in all of the 15 clinics.

- Dosage levels of methadone at admission are typically under 50 mg/day, with a usual maintenance dose of 50 mg/day or higher reported by seven clinics.

- Medical (67 percent) and psychological (27 percent) are the most common services reported received in clinical/medical records and by clients.

- Family, legal, education, employment, or financial services are not commonly recorded in files or reported by clients.

The variety of approaches to treatment and services provided makes any classification of outpatient methadone clinics difficult. Clearly, a simple description is inadequate to characterize methadone treatment. In subsequent analyses of TOPS data, attention will be given to developing a classification system for clinics and the mix of services provided to clients.

During the first 6 months of treatment in methadone programs, positive changes in behavior were reported by clients. Comparing self-reports of behaviors in the year (or 3 months for illegal activity) prior to treatment with reports during the first and second 3 months in treatment

shows that the proportion of clients reporting problems decreases.

- Weekly or greater use of the primary drug (typically heroin) declines from about 80 percent to between 8 and 16 percent.
- Drug related problems decrease from about 80 percent to between 17 and 28 percent.
- Indicators of depression are reported by almost 60 percent of clients before treatment and 27 and 31 percent during treatment.
- Commission of serious non-drug defined crimes is reduced from over 20 percent to less than 10 percent by the second 3 months in treatment (rate of commission is also reduced by a ratio of 5 to 1).
- Full-time employment shows a slight increase.

These results support previous studies that show methadone treatment does have a positive summative impact for clients remaining in the program. We feel that, in order to better understand how to make treatment more effective and efficient, we must conduct more formative analyses of the factors that are related to more positive outcomes.

Future TOPS analyses will be directed toward describing, characterizing, and assessing impacts of various types of approaches to treatment and services provided by clinics; and examining the combination of clients and treatment that produce more positive outcomes. In undertaking these analyses, we hope to provide information that can be used to generate hypotheses for future studies, design controlled studies of particular issues, and confirm results of controlled studies in a national survey sample of programs.

The use of this integrated research framework should provide very useful information for states, communities, agencies, and programs in designing more effective and efficient treatment services in outpatient methadone modalities/environments.

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